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L2 1362601 FILE MEDLINE
L3 453101 FILE CAPLUS
L4 910325 FILE EMBASE
L5 880891 FILE BIOSIS
L6 314514 FILE JICST-EPLUS
L7 40782 FILE WPIDS

TOTAL FOR ALL FILES

L8 3962214 (CANCER OR NEOPLASM OR TUMOR OR TUMOR)

=> s (l1 or urine) and l8
L9 18291 FILE MEDLINE
L10 7589 FILE CAPLUS
L11 12285 FILE EMBASE
L12 7040 FILE BIOSIS
L13 3607 FILE JICST-EPLUS
L14 707 FILE WPIDS

TOTAL FOR ALL FILES

Searched by: Mary Hale 308-4258 CM-1 12D16

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L15 49519 (L1 OR URINE) AND L8

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=> s l15 and (apc or antigen present? cell! or dendrit? cell!)

L18 13 FILE MEDLINE

L19 31 FILE CAPLUS

L20 12 FILE EMBASE

L21 5 FILE BIOSIS

L22 0 FILE JICST-EPLUS

L23 15 FILE WPIDS

TOTAL FOR ALL FILES

L24 76 L15 AND (APC OR ANTIGEN PRESENT? CELL! OR DENDRIT? CELL!)

=> s l24 and exosome?

L25 0 FILE MEDLINE

L26 0 FILE CAPLUS

L27 0 FILE EMBASE

L28 0 FILE BIOSIS

L29 0 FILE JICST-EPLUS

L30 0 FILE WPIDS

TOTAL FOR ALL FILES

L31 0 L24 AND EXOSOME?

=> s l15 and exosom?

L32 0 FILE MEDLINE

L33 0 FILE CAPLUS

L34 0 FILE EMBASE

L35 0 FILE BIOSIS

L36 0 FILE JICST-EPLUS

L37 0 FILE WPIDS

TOTAL FOR ALL FILES

L38 0 L15 AND EXOSOM?

=> dup rem l24

PROCESSING COMPLETED FOR L24

L39 50 DUP REM L24 (26 DUPLICATES REMOVED)

=> d 1-50 cbib abs

L39 ANSWER 1 OF 50 CAPLUS COPYRIGHT 2002 ACS

2002:10730 Document No. 136:49326 Diagnosis of diseases associated with the immune system using oligomer probes to detect cytosine methylation state. Olek, Alexander; Piepenbrock, Christian; Berlin, Kurt (Epigenomics A.-G., Germany). PCT Int. Appl. WO 2002000928 A2 20020103, 32 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2001-EP7537 20010702. PRIORITY: DE 2000-10032529 20000630; DE 2000-10043826 20000901.

AB The invention relates to chem. modified genomic sequences of genes assocd. with the immune system, an oligonucleotide directed against said sequence

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and/or PNA oligomers for the detection of the methylation state of cytosine of genes assocd. with the immune system. The present invention is based on the discovery that cytosine methylations patterns in genomic DNA are particularly suitable for diagnosis and/or therapy of diseases assocd. with the immune system. Thus, the chem. modified genomic sequences of genes assocd. with the immune system, and oligonucleotides and/or peptide nucleic acid oligomers for detecting the cytosine methylation state of immune system genes are provided. Specific reaction of bisulfite and subsequent alk. hydrolysis converts cytosine to uracil, which corresponds to thymidine in its base pairing behavior. However, 5-methylcytosine remains unmodified under these conditions. Consequently, the original DNA is converted in such a manner that methylcytosine, which originally could not be distinguished from cytosine by its hybridization behavior, can now be detected as the only remaining cytosine using "normal" mol. biol. techniques. The oligomer probes according to the present invention, contg. at least one CpG dinucleotide, constitute important and effective tools which make it possible to ascertain the genetic and epigenetic parameters of genes assocd. with apoptosis. The invention is exemplified by methylation anal. of gene DAPK1.

L39 ANSWER 2 OF 50 CAPLUS COPYRIGHT 2002 ACS

2002:31916 Document No. 136:82317 Methods of screening for disease by genetic assay after other diagnostic procedure. Berger, Barry M.; Laken, Steven J.; Lapidus, Stanley N. (USA). U.S. Pat. Appl. Publ. US 20020004206 A1 20020110, 8 pp., Cont.-in-part of U.S. Ser. No. 545,162. (English). CODEN: USXXCO. APPLICATION: US 2001-859990 20010517. PRIORITY: US 1999-PV128629 19990409; US 2000-545162 20000407.

AB The invention provides methods of screening for disease in a patient by performing a non-invasive or minimally invasive genetic assay on a sample from the patient to detect characteristics indicative of the presence of a disease in the sample at a predetd. time following the performance of a diagnostic procedure on a patient to detect characteristics indicative of the presence of a disease. Methods of this invention are useful in screening for **cancer**.

L39 ANSWER 3 OF 50 CAPLUS COPYRIGHT 2002 ACS

2002:143198 Method for inducing an anti-**tumor** and anti-cachexia immune response in mammals. Riordan, Neil H. (USA). U.S. Pat. Appl. Publ. US 20020022036 A1 20020221, 9 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-781023 20010209. PRIORITY: US 2000-PV226752 20000821.

AB The invention relates to inducing an immune response toward **tumor** assocd. antigens and in particular to the administration of high mol. wt. isolates of autologous **urine** either alone, with adjuvants, or with **antigen presenting cells**. The **antigen presenting cells** have been cocultured with isolates of autologous **urine**. The invention can also be used to treat cachexia in **cancer** or AIDS patients.

L39 ANSWER 4 OF 50 CAPLUS COPYRIGHT 2002 ACS

DUPLICATE 1

2001:185962 Document No. 134:234029 Methods for disease detection by determining the integrity of nucleic acids. Shuber, Anthony P. (Exact Laboratories, Inc., USA). PCT Int. Appl. WO 2001018252 A2 20010315, 44 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US24639 20000908. PRIORITY: US 1999-PV152847 19990908; US 1999-455950 19991207.

AB The present invention provides methods for detecting disease by anal. of a patient sample to det. the integrity of nucleic acids in the sample. DNA of stool samples was isolated by sequence-specific hybrid capture using biotinylated probes against portions of the BRCA1, BRCA2, p53, APC1, and APC2 genes. Fragments of the 5 different loci were amplified using

primers spaced 200, 400, 800, 1300, 1800, and 2400 base pairs apart. Each amplification was scored. Since five loci were interrogated using 6 primer pairs each, the max. score was 30. The cutoff for a pos. screen was set at 21.

L39 ANSWER 5 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
2001:115328 Document No. 134:173861 Methods for detecting mutations using primer extension. Shuber, Anthony P.; Pierceall, William (Exact Laboratories, Inc., USA). PCT Int. Appl. WO 2001011083 A2 20010215, 25 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US21763 20000809. PRIORITY: US 1999-371991 19990811.
AB Methods for detecting nucleotide deletions in biol. samples are described. Methods of the invention are particularly useful for detecting deletions in regions of polynucleotide repeats. In particular, methods of the invention are useful to detect deletions at the BAT26 locus.

L39 ANSWER 6 OF 50 CAPLUS COPYRIGHT 2002 ACS
2001:693569 Document No. 135:252749 Diagnosis of diseases associated with **tumor** suppressor genes and oncogenes using oligomer probes to detect cytosine methylation state. Olek, Alexander; Piepenbrock, Christian; Berlin, Kurt (Epigenomics A.-G., Germany). PCT Int. Appl. WO 2001068912 A2 20010920, 27 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP2955 20010315. PRIORITY: DE 2000-10013847 20000315; DE 2000-10019058 20000406; DE 2000-10019173 20000407; DE 2000-10032529 20000630; DE 2000-10043826 20000901.

AB The present invention is based on the discovery that cytosine methylations patterns in genomic DNA are particularly suitable for diagnosis and/or therapy of diseases assocd. with **tumor** suppressor genes. Thus, the chem. modified genomic sequences of genes assocd. with **tumor** suppressor genes and oncogenes, and oligonucleotides and/or peptide nucleic acid oligomers for detecting the cytosine methylation state of **tumor** suppressor genes and oncogenes are provided. Specific reaction of bisulfite and subsequent alk. hydrolysis converts cytosine to uracil, which corresponds to thymidine in its base pairing behavior. However, 5-methylcytosine remains unmodified under these conditions. Consequently, the original DNA is converted in such a manner that methylcytosine, which originally could not be distinguished from cytosine by its hybridization behavior, can now be detected as the only remaining cytosine using "normal" mol. biol. techniques. The oligomer probes according to the present invention, contg. at least one CpG dinucleotide, constitute important and effective tools which make it possible to ascertain the genetic and epigenetic parameters of genes assocd. with **tumor** suppressor genes and oncogenes. The invention is exemplified by methylation anal. of gene MYC.

L39 ANSWER 7 OF 50 CAPLUS COPYRIGHT 2002 ACS
2001:435304 Document No. 135:41000 Nucleic acid detection-based methods and kits for drug screening. Shuber, Anthony P. (Exact Sciences Corporation, USA). PCT Int. Appl. WO 2001042503 A2 20010614, 40 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US32387 20001128. PRIORITY: US 1999-PV169457 19991207.
AB The invention provides kits and methods for screening drugs and drug candidates for activity by detg. the presence or absence of high integrity

nucleic acid in a sample.

L39 ANSWER 8 OF 50 CAPLUS COPYRIGHT 2002 ACS

2001:338762 Document No. 134:362292 Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile. Farr, Spencer (Phase-1 Molecular Toxicology, USA). PCT Int. Appl. WO 2001032928 A2 20010510, 222 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US30474 20001103. PRIORITY: US 1999-PV165398 19991105; US 2000-PV196571 20000411.

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

L39 ANSWER 9 OF 50 CAPLUS COPYRIGHT 2002 ACS

2001:643389 Document No. 135:206431 Use of primer extension reactions in detecting mutations, and/or single nucleotide polymorphisms in genes associated with **cancer**, and/or disorders of the colon. Shuber, Anthony P.; Pierceall, William; Laken, Steven J. (USA). U.S. Pat. Appl. Publ. US 20010018180 A1 20010830, 23 pp., Cont.-in-part of U.S. Ser. No. 468,670. (English). CODEN: USXXCO. APPLICATION: US 2001-757949 20010110. PRIORITY: US 1999-PV134711 19990518; US 1999-371991 19990811; US 1999-468670 19991221.

AB The invention provides the use of primer extension reactions in detecting mutations, and/or single nucleotide polymorphisms in target regions (regions contg. repetitive sequences) of genes assocd. with **cancer**, and/or disorders of the colon. The invention relates that a labeled primer is hybridized upstream of the target region and is extended through the target region. The labeled extension product is then analyzed, and the size of product is indicative of the presence or absence of a mutation in target region. The invention also relates that target regions can be selected from a group of genes including **APC**, **DCC**, **p53**, or **RAS**, or the **BAT-26** segment of the **MSH2** gene. The invention further relates that the assay of the invention can be performed on heterogeneous samples obtained from patients by non-invasive or minimally-invasive methods. Such assays may be employed alone or in combination with other disease screening techniques. In the example section, the primer extension reaction assay was used to detect deletion mutations in the **BAT-26** and **APC** loci, and was used in **cancer** diagnosis.

L39 ANSWER 10 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-582004 [65] WPIDS
CR 1998-531576 [45]
AB WO 200162271 A UPAB: 20020109

NOVELTY - An oligonucleotide (I) having a complementary sequence to a fully defined sequence (S1) of 1783 base pairs (bp) as given in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) treating a neoplastic state in an individual in need of such treatment comprising administering an effective dose of (I);

(2) screening for compounds that inhibit hepsin activity comprising:

(a) contacting a hepsin protein containing sample with a compound;

and

(b) assaying for hepsin protease activity, where a decrease in hepsin protease activity in the presence of the compound relative to hepsin protease activity in the absence of the compound is indicative of a compound that inhibits hepsin activity;

(3) diagnosing (M1) **cancer** in an individual comprising detecting hepsin in a biological sample from the individual, where the presence of hepsin in the sample is indicative of the presence of **cancer** in the individual;

(4) detecting (M2) malignant hyperplasia in a biological sample comprising isolating mRNA from the sample and detecting hepsin mRNA in the sample, where the presence of hepsin mRNA is indicative of the presence of malignant hyperplasia;

(5) detecting (M3) malignant hyperplasia in a biological sample comprising isolating protein from the sample and detecting hepsin protein in the sample, where the presence of hepsin in the sample is indicative of the presence of malignant hyperplasia in the individual;

(6) inhibiting expression of endogenous hepsin in a cell comprising introducing a vector into a cell, where the vector containing a hepsin gene in opposite orientation operably linked to elements necessary for expression, where expression of the vector in the cell produces hepsin antisense mRNA which hybridizes to endogenous hepsin mRNA thereby inhibiting expression of endogenous hepsin in the cell;

(7) inhibiting hepsin protein in a cell comprising introducing a hepsin specific antibody into a cell, where binding of the antibody to the protein inhibits the protein;

(8) targeted therapy (M4) to an individual comprising administering a compound which has a hepsin specific targeting group and a therapeutic group;

(9) vaccinating (M5) an individual against hepsin comprising inoculating an individual with a hepsin protein or its fragment, where the protein (fragment) lack protease activity and inoculation elicits an immune response in the individual; and

(10) producing (M6) immune-activated cells directed towards hepsin comprising exposing **dendritic cells** to a hepsin protein (fragment) which lacks protease activity, where exposure to the hepsin protein (fragment) activates the **dendritic cells**

ACTIVITY - Cytostatic. No supporting data is given.

MECHANISM OF ACTION - Vaccine.

USE - The oligonucleotide is useful for the detection of **cancer**, treatment of **cancer** and screening for compounds that inhibit hepsin activity. Hepsin protease, mRNA and immunospecific anti-hepsin antibodies are useful for the diagnosis of **cancer** in an individual (all claimed).

Dwg.0/16

L39 ANSWER 11 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-541652 [60] WPIDS

AB WO 200161028 A UPAB: 20011018

NOVELTY - Determining, (D1), the sequence of a polynucleotide comprising providing a nucleic acid fragment, (F), having a homology of a known reference sequence, (RF), expressing at least one polypeptide, (P), from it and assessing at least one physical property of at least one P to determine the sequence of F, by comparing a property to the predicted properties of a P encoded by RF, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

- (1) genetic analysis comprising D1;
- (2) assessment of a disease;
- (3) assessment of a disease, condition, genotype or phenotype comprises D1 and correlating the determined sequence with the disease, condition, genotype or phenotype;
- (4) diagnostic or prognostic test for a disease, condition, genotype or phenotype comprises D1;
- (5) assessment of a disease, condition, genotype or phenotype;
- (6) diagnosis or prognosis of a disease, condition, genotype or phenotype;
- (7) a data structure useful for detecting and analyzing DNA polymorphisms;
- (8) a computer storage medium;
- (9) a computer implemented method to identify an F encoding P, where F is a fragment of RF. The F is of known RF.
- (10) a relational data set is useful for detecting and analyzing DNA mutations and polymorphisms;
- (11) a computer program for searching for the data set of (10);
- (12) genetic analysis comprising:
 - (i) providing two or more nucleic acids samples derived from two or more heterogeneous biological samples;
 - (ii) expressing polypeptides from each nucleic acid sample;
 - (iii) subjecting P, in combination, to physical property assessment;and
- (iv) comparing the results of the physical property assessment to the predicted properties encoded in at least one RF; and
- (13) providing a nucleic acid molecule.

USE - The method, D1, has application for the detection of, diagnosis or prognosis of genetic disease. The diseases include Alzheimer's disease, Ataxia talangietasia, familial adenomatous polyposis, hereditary breast and ovarian **cancer**, HNPCC, retinoblastoma, Wilm's **tumor**, Li-Fraumeni syndrome, endocrine neoplasia, Von Hippel-Lindau syndrome, congenital adrenal hyperpalsia, androgen receptor deficiency, tetrahydrobiopterin deficiency, X-linked agammaglobulinemia, Cystic Fibrosis, diabetes, muscular dystrophy, Factor X deficiency, mitochondrial gene deficiency and Factor VII deficiency. The loci include ATM, **APC**, BRCA1, BRCA2, CDK2, CDKN2, hMSH2, hMLH1, hPMS1, hPMS2, RB1, WT1, p53, MEN1, MEN2, VHL, CFTR, DMD, BMD and RP.

Dwg.0/0

L39 ANSWER 12 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-514676 [56] WPIDS

CR 1998-531576 [45]

AB WO 200159158 A UPAB: 20011227

NOVELTY - Diagnosing **cancer** (M1) comprises detecting stratum corneum chymotrypsin enzyme (I).

DETAILED DESCRIPTION - Diagnosing **cancer** (M1) comprises:

- (a) obtaining a biological sample; and
- (b) detecting stratum corneum chymotrypsin enzyme (I), where the presence of (I) is indicative of the presence of **cancer**.

INDEPENDENT CLAIMS are also included for the following:

- (1) a method (M2) for detecting malignant hyperplasia in a sample comprising:

(a) isolating mRNA from the sample; and
 (b) detecting the mRNA of (I);
 (2) a method (M3) for detecting malignant hyperplasia in a sample comprising:
 (a) isolating protein from the sample; and
 (b) detecting the protein of (I);
 (3) a method (M4) for inhibiting expression of endogenous (I) in a cell comprising introducing a vector (II) into a cell, where (II) comprises a gene encoding (I) in opposite orientation linked to elements necessary for expression, where expression of (II) produced antisense mRNA of (I) which hybridizes to endogenous mRNA of (I) to inhibit its expression;
 (4) a method (M5) of inhibiting (I) in a cell comprising introducing an antibody (III) specific for (I), where binding of (III) inhibits (I);
 (5) a method (M6) of targeted therapy comprising administering a compound which has a targeting moiety and a therapeutic moiety where the therapeutic moiety is specific for (I);
 (6) a method (M7) of vaccinating against (I) comprising inoculating with (I) or its fragment which lacks protease activity and elicits an immune response;
 (7) a method (M8) of producing immune-activated cells directed towards (I) comprising exposing **dendritic cells** to (I) or its fragment which lacks protease activity in order to activate the **dendritic cells**;
 (8) an oligonucleotide (IV) having a sequence complementary to the fully defined 969 base pair sequence given in the specification (N1);
 (9) a composition comprising (IV); and
 (10) a method (M9) of screening for compounds that inhibit (I) comprising:
 (a) contacting a sample which comprises (I) with a compound; and
 (b) assaying for activity of (I), where a decrease in activity in the presence of the compound compared to the activity in the absence of the compound is indicative that the compound inhibits (I).

ACTIVITY - Cytostatic.

No supporting data given.

MECHANISM OF ACTION - Vaccine; antisense therapy (claimed).

No supporting data given.

USE - The method is useful for diagnosing **cancer** (claimed).

The oligonucleotide (IV) may be used to treat a **cancer** selected from ovarian, breast, lung, colon, prostate and other **cancers** in which (I) is overexpressed (claimed).

Dwg.0/19

L39 ANSWER 13 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-496835 [54] WPIDS

CR 1998-531576 [45]

AB WO 200154712 A UPAB: 20011220

NOVELTY - Diagnosing **cancer** in an individual comprising:

(a) obtaining a biological sample from an individual; and
 (b) detecting PUMP-1 (undefined) protease in the sample, where the presence of PUMP-1 in the sample is indicative of the presence of **cancer** in the individual and the absence of PUMP-1 in the individual is indicative of the absence of **cancer** in the individual, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) detecting malignant hyperplasia comprising isolating mRNA or protein from the sample and detecting PUMP-1 mRNA or protein in the sample, where the presence of PUMP-1 in the sample is indicative of the presence of malignant hyperplasia in the individual and the absence of PUMP-1 in the individual is indicative of the absence of malignant hyperplasia in the individual;

(2) inhibiting expression of endogenous PUMP-1 in a cell comprising introducing a vector into a cell, where the vector comprises a PUMP-1 gene in opposite orientation operably linked to elements necessary for expression, where expression of the vector in the cell produces PUMP-1 antisense mRNA, and where the PUMP-1 antisense mRNA hybridizes to endogenous PUMP-1 mRNA, thus inhibiting expression of endogenous PUMP-1 in the cell;

(3) inhibiting PUMP-1 protein in a cell comprising introducing an antibody into a cell, where the antibody is specific for a PUMP-1 protein or its fragment, and binding of the antibody to the PUMP-1 protein inhibits the PUMP-1 protein;

(4) targeted therapy to an individual comprising administering a compound to an individual, where the compound has a targeting group and a therapeutic group, where the targeting group is specific for PUMP-1;

(5) vaccinating an individual against PUMP-1 comprising inoculating an individual with a PUMP-1 protein or its fragment, where the PUMP-1 protein or its fragment lack PUMP-1 protease activity, where the inoculation with the PUMP-1 protein or its fragment elicits an immune response in the individual against PUMP-1;

(6) producing immune-activated cells directed toward PUMP-1 comprising exposing **dendritic cells** to a PUMP-1 protein or its fragment, where the PUMP-1 protein or its fragment lacks PUMP-1 protease activity, and where the exposure to the PUMP-1 protein or its fragment activates the **dendritic cells**, thus producing immune-activated cells directed toward PUMP-1;

(7) an oligonucleotide having a sequence complementary to a fully defined 1078-base pair (bp) DNA sequence as given in the specification;

(8) treating a neoplastic state in an individual in need of such treatment comprising administering to the individual the oligonucleotide;

(9) screening for compounds that inhibit PUMP-1 activity comprising:

(a) contacting a sample with a compound, where the sample comprises PUMP-1 protein; and

(b) assaying for PUMP-1 protease activity, where a decrease in the PUMP-protease activity in the presence of the compound relative to PUMP-1 protease activity in the absence of the compound indicatives the compound inhibits PUMP-1 activity and

(10) detecting ovarian malignant hyperplasia in a biological sample comprises:

(a) isolating the proteases or protease mRNA present in the biological sample; and

(b) detecting specific proteases or protease mRNA present in the biological sample, where the proteases are hepsin, protease M, complement factor B, stratum corneum chymotrypsin enzyme (SCCE), other serine proteases, cathepsin L or PUMP-1.

ACTIVITY - Cytostatic. No supporting data is given.

MECHANISM OF ACTION - Gene therapy; vaccine.

USE - The method is useful for the early detection or diagnosis of ovarian **cancer** and other neoplastic state or malignancies (e.g. lung **cancer**, prostate **cancer**, colon **cancer** or other **cancers** in which PUMP-1 is overexpressed). The method is also useful for diagnosing whether an individual has **cancer**, is suspected of having **cancer** or is at risk of getting **cancer**. The PUMP-1 proteins are also useful for vaccinating against neoplastic states. The oligonucleotide is useful for treating a neoplastic state such as lung **cancer**, prostate **cancer**, colon **cancer** or other **cancers** in which PUMP-1 is overexpressed (all claimed).

Dwg.0/21

NOVELTY - An isolated nucleic acid molecule (I) encoding antigen presenting cell expression (APEX)-1, APEX-2 or APEX-3 protein, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated protein (II) designated APEX-1 or APEX-2, comprising an extracellular domain having one immunoglobulin (Ig)-like structure and N-glycosylation site, transmembrane domain, and cytoplasmic domain having at least one SH2-binding motif, or APEX-3 comprising 1(met)-285(pro) amino acids of a sequence (S1) comprising 285 amino acids fully defined in the specification

(2) an isolated polynucleotide variant (IIa) having at least 70% identity to (I), a polynucleotide which hybridizes under stringent conditions to the complement of (I), or a nucleic acid molecule comprising a nucleotide sequence complementary to (I);

(3) a vector (III) comprising (I);

(4) a host vector system (IV) comprising (III) in a suitable host cell;

(5) an antibody (Ab) which recognizes and binds to (II) or its fragment having APEX activity;

(6) a Fab', F(ab)2', or Fv fragment of Ab;

(7) producing an APEX protein;

(8) an APEX protein (VI) produced by the above said method;

(9) a soluble APEX protein (VII) having a first amino acid sequence corresponding to an extracellular domain of an APEX protein and a second amino acid sequence corresponding to a functional group that alters the solubility of the APEX protein;

(10) identifying a molecule in a sample which specifically binds to (VII), by contacting the APEX protein with the sample under suitable conditions so as to obtain a complex having the APEX protein and the molecule, recovering the complex and separating the APEX protein from the molecule in the complex and identifying the separated molecule; and

(11) a nucleic acid molecule having a nucleotide sequence selected from any one of the 36 sequences fully defined in the specification.

ACTIVITY - Antiasthmatic; antipsoriatic; antidiabetic; anti-HIV; hepatotropic; antiarteriosclerotic; antiinflammatory; dermatological; antianemic; immunosuppressive; neuroprotective; osteopathic; antiarthritic; uropathic; antirheumatic; cytostatic.

MECHANISM OF ACTION - Gene therapy; vaccine. No supporting data given.

USE - APEX proteins and antibodies are useful in the study, diagnosis, prevention and treatment of disease associated with the presence of an APEX protein e.g., asthma, arteriosclerosis, AIDS, cirrhosis, Crohn's disease, atopic dermatitis, autoimmune anemia, bursitis, cholecystitis, diabetes mellitus, emphysema, atrophic gastritis, inflammatory bowel disease, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, psoriasis, Reiter's syndrome, rheumatoid arthritis, inflammation, **cancer**, immune disorders, autoimmune diseases, graft rejections, graft versus host reaction and systemic lupus erythematosus. APEX proteins are useful as diagnostic and/or prognostic markers on APCs or APEX expressing cells, the ability to elicit the generation of antibodies and as targets for various therapeutic modalities. APEX proteins are also useful for identifying and isolating ligand that bind APEX. Ab is useful in diagnostic assays and imaging methodologies, for purifying APEX protein and for generating large quantities of APEX-positive cells.

Dwg.0/16

L39 ANSWER 15 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-381031 [40] WPIDS

AB WO 200129056 A UPAB: 20010719

NOVELTY - DNA (I) encoding an extracellular serine protease, termed **tumor** antigen-derived gene 15 (TADG-15) protein (or a DNA encoding

TADG-15 protein which hybridizes under high stringency conditions to (I) or an isolated DNA encoding a TADG-15 protein differing from (I) in codon sequence due to the degeneracy of the genetic code), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) a vector (II) comprising (I);
- (2) a host cell (III) transfected with (II) and expressing TADG-15 protein;
- (3) an isolated and purified TADG-15 protein coded by (I);
- (4) detecting TADG-15 mRNA in a sample, by contacting a sample with a probe specific for TADG-15 and detecting binding of the probe to TADG-15 mRNA in the sample;
- (5) a kit for detecting TADG-15 mRNA or protein comprising an oligonucleotide probe or an antibody specific for TADG-15;
- (6) an antibody (IV) specific for TADG-15 protein or its fragments;
- (7) screening for compounds that inhibit TADG-15, by contacting the sample comprising TADG-15 protein with a compound and assaying for TADG-15 protease activity, where a decrease in TADG-15 protease activity in the presence of the compound relative to TADG-15 protease activity in the absence of the compound is indicative of a compound that inhibits TADG-15;
- (8) a targeted therapy (M1) to an individual, by administering a compound having a targeting moiety, specific for TADG-15 and a therapeutic moiety;
- (9) diagnosing (M2) **cancer** in an individual, by obtaining a biological sample from the individual and detecting TADG-15 in the sample, where the presence and absence of TADG-15 in the sample is indicative of the presence and absence of carcinoma in the individual;
- (10) producing (M3) immune-activated cells directed towards TADG-15, by exposing **dendritic cells** to a TADG-15 protein or its fragment lacking TADG-15 protease activity, which activates the **dendritic cells** and produces immune-activated cells directed towards TADG-15;
- (11) an immunogenic composition comprising an immunogenic fragment of a TADG-15 protein and an adjuvant;
- (12) an oligonucleotide (V) having a nucleotide sequence complementary to (I); and
- (13) a composition comprising (V).

ACTIVITY - Cytostatic. No supporting data is given.

MECHANISM OF ACTION - Vaccine; Antisense therapy.

USE - TADG-15 protein or its fragments of 9-20 residues that lacks TADG-15 protease activity is useful for vaccinating an individual against TADG-15, having, suspected of having or at risk of getting **cancer**. (V) is useful for treating neoplastic state, like ovarian, breast, lung, colon, prostate and other **cancers** in which TADG-15 is overexpressed. (IV) is useful for detecting TADG-15 protein in a biological sample from an individual susceptible of having **cancer** and also for treating the above conditions. (II) and (IV) are useful for inhibiting the expression of TADG-15 protein in a cell (claimed). TADG-15 protein is useful in diagnosing **cancer** in different tissues since it is highly overexpressed in **tumor** cells.
Dwg.0/12

L39 ANSWER 16 OF 50 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:513136 Document No.: PREV200100513136. Phase I study of intravesical vaccinia virus as a vector for gene therapy of bladder **cancer**.

Gomella, Leonard G. (1); Mastrangelo, Michael J. (1); McCue, Peter A. (1); Maguire, Henry C., Jr. (1); Mulholland, S. Grant (1); Lattime, Edmund C. (1) Departments of Urology, Pathology and Medicine (Division of Medical Oncology), Jefferson Medical College and Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA USA. Journal of Urology, (October, 2001) Vol. 166, No. 4, pp. 1291-1295. print. ISSN: 0022-5347. Language: English. Summary Language: English.

AB Purpose: Vaccinia virus is a DNA poxvirus previously used as a vaccine to eradicate smallpox. The virus has a high efficiency of infection, replicates in the cytoplasm without chromosomal integration and can transport a large amount of recombinant DNA without losing infectivity. Therefore, it is an excellent choice as a vector for gene delivery in vivo. Large quantities of vaccinia have been injected into dermal, subcutaneous and peripheral lymph node melanoma metastases without significant side effects, and with efficient infection of the **tumor** cells and recombinant gene transfection. To determine if vaccinia, when given intravesically, can effectively infect bladder mucosa and **tumor** with acceptable toxicity, we performed a phase I trial of intravesical vaccinia in patients with muscle invasive transitional cell carcinoma before radical cystectomy. Materials and Methods: After documenting immune competence and demonstration of a major reaction after revaccination, patients received 3 increasing doses of intravesical Dryvax vaccinia virus (Wyeth-Ayerst Laboratories, Philadelphia, Pennsylvania) that was provided by the Centers for Disease Control. Approximately 24 hours after the third dose, cystectomy was performed and the tissue was examined microscopically. Results: There were 4 patients who were treated. The 3 patients who received the highest doses (100X10⁶ plaque forming units) had significant mucosal and submucosal inflammatory infiltration by lymphocytes, eosinophils, and plasma cells into **tumor** and normal tissue. **Dendritic cells** were recruited to the site after exposure to the vaccinia. Significant mucosal edema and vascular ectasia were seen. **Tumor** and normal urothelial cells showed evidence of viral infection, including enlarged vacuolated cells with cytoplasmic inclusions. There were no clinical or laboratory manifestations of vaccinia related toxicity except mild dysuria. Of the 4 patients 3 survived and were free of disease at 4-year followup. Conclusions: Our study demonstrates that vaccinia virus can be administered safely into the bladder with recruitment of lymphocytes and induction of a brisk local inflammatory response. To our knowledge, this is the first report of direct delivery of live virus into the human bladder. The role of wild type vaccinia as immunotherapy for bladder **cancer** warrants further study. Furthermore, these data support the exploration of recombinant vaccinia as a putative gene therapy vector for intravesical infection and transfection of bladder **tumor** cells with cytokine or other genes, an approach that our group pioneered and most recently studied in patients with superficial melanoma.

L39 ANSWER 17 OF 50 CAPLUS COPYRIGHT 2002 ACS

2001:426731 Document No. 136:148631 Lymphoepithelioma-like carcinoma of the urinary bladder: a clinicopathologic study of 13 cases. Lopez-Beltran, Antonio; Luque, Rafael J.; Vicioso, Luis; Anglada, Francisco; Requena, Maria J.; Quintero, Ana; Montironi, Rodolfo (Facultad de Medicina, Department of Pathology, Reina Sofia University Hospital and Cordoba University Medical School, Cordoba, 14004, Spain). Virchows Archiv, 438(6), 552-557 (English) 2001. CODEN: VARCEM. ISSN: 0945-6317. Publisher: Springer-Verlag.

AB Lymphoepithelioma-like carcinoma (LELCA) of the urinary bladder is a rare variant of bladder **cancer** characterized by a malignant epithelial component densely infiltrated by lymphoid cells. It is characterized by indistinct cytoplasmic borders and a syncytial growth pattern. These **neoplasms** deserve recognition and attention, chiefly because they may be responsive to chemotherapy. We report on the clinicopathol. features of 13 cases of LELCA recorded since 1981. The chief complaint in all 13 patients was hematuria. Their ages ranged from 58 yr to 82 yr. All **tumors** were muscle invasive. A significant lymphocytic reaction was present in all of these **tumors**. There were 3 pure LELCA and 6 predominant LELCA with a concurrent transitional cell carcinoma (TCC). The remainder four cases had a focal LELCA component admixed with TCC. Immunohistochem. showed LELCA to be reactive

against epithelial membrane antigen and several cytokeratins (CKs; AE1/AE3, AE1, AE3, CK7, and CK8). CK20 and CD44v6 stained focally. The lymphocytic component was composed of a mixt. of T and B cells intermingled with some **dendritic cells** and histiocytes. Latent membrane protein 1 (LMP1) immunostaining and in situ hybridization for Epstein-Barr virus were neg. in all 13 cases. DNA ploidy of these **tumors** gave DNA histograms with diploid peaks (n=7) or non-diploid peaks (aneuploid or tetraploid; n=6). All patients with pure and 66% with predominant LELCA were alive, while all patients having focal LELCA died of disease. These data suggest that pure and predominant LELCA of the bladder appear to be morphol. and clin. different from other bladder (undifferentiated and poorly differentiated conventional TCC) carcinomas and should be recognized as sep. clinicopathol. variants of TCC with heavy lymphocytic reaction relevant in patient management.

L39 ANSWER 18 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
 2000:824455 Document No. 133:361650 Diagnostic detection of colorectal disease based on mutations in the BAT-26 segment of the MSH2 mismatch repair gene. Laken, Steven (Exact Laboratories, Inc., USA). PCT Int. Appl. WO 2000070096 A2 20001123, 23 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US13655 20000518. PRIORITY: US 1999-PV134711 19990518; US 1999-468670 19991221.

AB Methods of the invention comprise assays for markers indicative of **cancer**, precancer, and other colonic or colorectal diseases or disorders. The methods exploit the discovery that mutations in the BAT-26 segment of the MSH2 mismatch repair gene are closely assocd. with inherited **cancers** (and pre-cancerous lesions); in particular, BAT-26 mutations are highly assocd. with hereditary non-polyposis colorectal **cancer** in >90% of patients. Thus, BAT-26 is an ideal marker for screening assays to detect this colorectal **cancer**, or colorectal adenoma that may or may not develop into **cancer**. Assays of the invention are preformed on heterogeneous samples obtained from patients by non-invasive or minimally-invasive methods. Such assays may be employed alone or in combination with other disease screening techniques.

L39 ANSWER 19 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
 2000:707333 Document No. 133:280147 Methods for improving sensitivity and specificity of assays screening for cancerous or pre-cancerous conditions. Lapidus, Stanley N.; Shuber, Anthony P. (Exact Laboratories, Inc., USA). PCT Int. Appl. WO 2000058514 A2 20001005, 38 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US7882 20000324. PRIORITY: US 1999-277016 19990326.

AB Methods of the invention comprise assays for markers indicative of **cancer** or precancer. Assays of the invention are performed on samples obtained from a patient by non-invasive or minimally-invasive methods. The invention provides nucleic acid indicia of **cancer** or precancer with high sensitivities and high specificities for detection. Criteria for design and selection of primers and probes for diagnosis of specific forms of **cancer** are given. Primers and probes for the detection of mutations in the c-Ki-ras, **APC** and p53 genes in the diagnosis of colon **cancers** is demonstrated. DNA from stool samples was captured with gene specific probes and amplified by PCR with allele-specific primers. Detection of alleles of these genes in combination with mutation in the Bat-26 colorectal **cancer** marker gene had a sensitivity of detection of up to 90% and a specificity of 100%.

L39 ANSWER 20 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5

2000:493764 Document No. 133:117176 Immunoassays to detect diseases or disease susceptibility traits. Boman, Bruce M. (Catx, Inc., USA). PCT Int. Appl. WO 2000042436 A1 20000720, 69 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US635 20000111. PRIORITY: US 1999-PV116247 19990114.

AB Disclosed are immunoassay methods for the diagnosis/prognosis of diseases and disease susceptibility traits assocd. with gene mutations that cause protein truncation or allelic loss. The levels of one or more targeted wild-type proteins expressed by a subject gene or genes are immunol. quantitated in biol. samples. Results indicating that a targeted wild-type protein is not present in an assayed sample, or that approx. 50 % of the normal amt. of such a wild-type protein is present in an assayed sample are considered to be pos. for a mutation in one or both alleles of a subject gene, and correlated with the disease or the disease susceptibility trait assocd. with that mutation or mutations. Normal cells, particularly normal peripheral blood lymphocytes, are preferred biol. samples.

L39 ANSWER 21 OF 50 CAPLUS COPYRIGHT 2002 ACS

2000:368646 Document No. 133:13383 Single-base primer extension methods utilizing donor and acceptor molecules for detecting rare alleles and their diagnostic use. Lapidus, Stanley N.; Shuber, Anthony P. (Exact Laboratories, Inc., USA). PCT Int. Appl. WO 2000031305 A2 20000602, 29 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US27804 19991123. PRIORITY: US 1998-PV109599 19981123.

AB Methods are provided for selective nucleic acid sequence detection in primer extension reactions of high specificity. These methods are useful for detecting small amts. of mutant nucleic acid in a heterogeneous biol. sample. These methods are particularly useful for identifying individuals with gene mutations indicative of early colorectal **cancer**. The method involves using a primer that hybridizes adjacent to a possible mutation site and a set of dideoxynucleotides, with each labeled with a different reporter group. By detg. which of the dideoxynucleotides is incorporated, the nature and frequency of the mutant allele can be detd.

L39 ANSWER 22 OF 50 CAPLUS COPYRIGHT 2002 ACS

2000:784326 Document No. 133:346755 Methods for improving sensitivity and specificity of screening assays. Lapidus, Stanley N.; Shuber, Anthony P. (Exact Laboratories, Inc., USA). U.S. US 6143529 A 20001107, 18 pp., Cont.-in-part of U.S. 5,928,870. (English). CODEN: USXXAM. APPLICATION: US 1999-277016 19990326. PRIORITY: US 1996-700583 19960814; US 1997-876857 19970616.

AB Methods of the invention comprise assays for markers indicative of **cancer** or precancer. Assays of the invention are performed on samples obtained from a patient by non-invasive or minimally-invasive methods. The invention provides nucleic acid indicia of **cancer** or precancer with high sensitivities and high specificities for detection.

L39 ANSWER 23 OF 50 CAPLUS COPYRIGHT 2002 ACS

2000:83154 Document No. 132:119575 Isolation of **cancer** cells from body fluids by filtration. Giesing, Michael (Germany). Ger. Offen. DE 19833738 A1 20000203, 10 pp. (German). CODEN: GWXXBX. APPLICATION: DE 1998-19833738 19980727.

AB The invention concerns the sepn. of **cancer** cells from body

fluids using 17-30 .mu.m pore filters; treating the isolated cells with guanidineisothiocyanate and phenol; and using the isolated DNA/RNA for amplification of **tumor** specific and **tumor** assocd. genes to diagnose dissemination and metastasis. Heparanized blood fraction contg. mononuclear cells was filtered through a 20 .mu.m polyethylene filter, the filter with the cells was incubated with Trizol for further DNA/RNA isolation.

L39 ANSWER 24 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2000-431666 [37] WPIDS

AB WO 200036414 A UPAB: 20000807

NOVELTY - A method (M1) for determining the sequence of a polynucleotide comprising expressing a polypeptide (P1) from a nucleic acid (N1) incorporated into a hybrid artificial gene and assessing at least 1 physical property of P1 to determine the sequence of N1 by comparing with a control, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) P1 used in M1;
- (2) a data structure useful for detecting and analyzing DNA mutations and polymorphisms comprising:
 - (a) data representing the following stored in a computer readable physical medium:
 - (i) a number of DNA sequence fragments contained within a reference DNA sequence;
 - (ii) polypeptides encoded by the sequences of (i); and
 - (iii) the predicted sequences of a number of polypeptides encoded in a set of transformed DNA sequence fragments, each member of the set comprised of a DNA sequence related to the fragment by a specific change selected from a single or multiple nucleotide polymorphism, substitution, deletion, or insertion, a DNA duplication, DNA inversion, and a DNA translocation;
 - (b) means for comparing the predicted sequences of the polypeptides with a test sequence;
- (3) a computer implemented method (M2) for determining the identity of a nucleic acid fragment encoding a polypeptide where the nucleic acid fragment is a fragment of a known reference sequence comprising:
 - (a) measuring a physical property of the polypeptide;
 - (b) comparing, in a computer, the measured physical property with a data set representing the predicted corresponding physical properties of possible polypeptides that are encoded by fragments of the reference sequence; and
 - (c) identifying a match between the measured physical property and a predicted physical property in the data set; and
- (4) a computer program comprising a search of the data structure of (2) (a).

USE - The method is useful for analysis of nucleic acid sequences, particularly for detecting various diseases e.g. Alzheimer's, familial adenomatous polyposis (**APC**), hereditary breast/ovarian **cancer**, hereditary melanoma, congenital adrenenal hyperplasia, androgen receptor deficiency, cystic fibrosis, diabetes.

ADVANTAGE - The method analyzes peptides (i.e. peptide reporters) which are more readily distinguished on the basis of mass compared to DNA sequences.

Dwg.0/0

L39 ANSWER 25 OF 50 MEDLINE

2000410754 Document Number: 20273374. PubMed ID: 10815927. Metabolism of irinotecan (CPT-11) by CYP3A4 and CYP3A5 in humans. Santos A; Zanetta S; Cresteil T; Deroussent A; Pein F; Raymond E; Vernillet L; Risse M L; Boige V; Gouyette A; Vassal G. (Centre National de Recherche Scientifique, Unite Mixte de Recherche 8532, Villejuif, France.) CLINICAL CANCER RESEARCH,

(2000 May) 6 (5) 2012-20. Journal code: C2H; 9502500. ISSN: 1078-0432.
Pub. country: United States. Language: English.

AB 7-Ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin (CPT-11), a DNA topoisomerase I inhibitor, undergoes several metabolic pathways to generate conjugated and unconjugated derivatives that could be excreted from the body. The objective of this study was to determine the oxidative metabolites of CPT-11 recovered in human **urine** samples and to identify cytochrome P450 (CYP) involved in their formation. In addition to the already known metabolites of CPT-11 [SN-38, SN-38-G, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (**APC**), and 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecin (NPC)], we isolated three oxidized metabolites from the **urine** of two children and two adults given CPT-11. M1 and M2 (molecular weight, 602) were hydroxylated, respectively, on the CPT moiety and on the terminal piperidine ring of CPT-11. M3 had a molecular mass of 602, but its **urine** concentration in patients was too low to establish its chemical structure by liquid chromatography/mass spectrometry. In vitro incubations with cells expressing CYP2C8, CYP2C9, CYP1A1, CYP1A2, or CYP3A7 did not produce any detectable metabolites. Only CYP3A4 produced both **APC** and NPC, resulting from the oxidation of the piperidinylpiperidine side chain of CPT-11 along with metabolite M2. The metabolism of CPT-11 by CYP3A5 was markedly different because neither **APC** or NPC nor M2 was produced, whereas only one new metabolite, M4 (molecular weight, 558), was generated by de-ethylation of the CPT moiety. No previous study has reported the presence of the M4 metabolite. Production of **APC**, NPC, M2, and M4 was prevented by ketoconazole, a specific CYP3A inhibitor. The parameters of CPT-11 biotransformation into M2 and M4 were examined using cell lines expressing, respectively, with CYP3A4 and CYP3A5, indicating that CPT-11 is preferentially metabolized by CYP3A4. In conclusion, CYP3A plays a major role in the metabolism of CPT-11, with some differences of the metabolic profile exhibited by 3A4 and 3A5.

L39 ANSWER 26 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
2001:83608 Document No. 135:32047 Cortisol producing adrenal adenoma - a new manifestation of Gardner's syndrome. Beuschlein, F.; Reincke, M.; Koniger, M.; D'Orazio, D.; Dobbie, Z.; Rump, L. C. (Schwerpunkt Endokrinologie, Abteilung Innere Medizin II, Germany). Endocr. Res., 26(4), 783-790 (English) 2000. CODEN: ENRSE8. ISSN: 0743-5800. Publisher: Marcel Dekker, Inc..

AB Familial adenomatous polyposis (FAP) is an autosomal dominant disorder which typically presents with colorectal **cancer** in early adult life secondary to extensive adenomatous polyps of the colon. Gardner's syndrome is a variant of FAP in which desmoid **tumors**, osteomas and pigmented retinal lesions occur together with intestinal manifestations. The **APC** gene (adenomatous polyposis coli) at 5q21 is a **tumor** suppressor gene which is mutant in FAP. A 36 yr old woman presented with a history of polyposis ventriculi, ovarian desmoid cysts, and disseminated desmoid **tumors**. Her familial history was unremarkable. On admission she complained wt. gain, secondary amenorrhea, and episodes of hypertension followed by paroxysmal headache. Elevated urinary free cortisol (878 .mu.g/24h), suppressed basal ACTH (< 5 pg/mL) and insuppressible serum cortisol after low dose dexamethasone (189 ng/mL) revealed adrenal Cushing's syndrome. Abdominal NMR showed an adrenal mass two centimeter in diam. with inhomogeneous contrast enhancement. Unilateral adrenalectomy was performed and an adrenal adenoma was diagnosed by histol. criteria. For mutational detection DNA from peripheral blood leukocytes was extd. A protein truncation test was performed, which revealed a termination mutation between codon 1099 and 1623 of the **APC** gene. Direct sequencing showed a point mutation in exon 15 of the **APC** gene at position 1542 (CAG .fwdarw. TAG). This region is known to be altered in patients with extraintestinal

manifestation of FAP. In patients with Gardner's syndrome adrenal **tumors** leading to hormonal excess should be considered. Whether mutations in the **APC** gene have implications in sporadic adrenal tumorigenesis needs to be proven.

L39 ANSWER 27 OF 50 MEDLINE DUPLICATE 7

2000191720 Document Number: 20191720. PubMed ID: 10725311.

Pharmacokinetics, metabolism, and excretion of irinotecan (CPT-11) following I.V. infusion of [(14)C]CPT-11 in **cancer** patients. Slatter J G; Schaaf L J; Sams J P; Feenstra K L; Johnson M G; Bombardt P A; Cathcart K S; Verburg M T; Pearson L K; Compton L D; Miller L L; Baker D S; Pesheck C V; Lord R S 3rd. (Pharmacia & Upjohn Company, Kalamazoo, Michigan 49007, USA.. john.g.slatter@am.pnu.com) . DRUG METABOLISM AND DISPOSITION, (2000 Apr) 28 (4) 423-33. Journal code: EBR; 9421550. ISSN: 0090-9556. Pub. country: United States. Language: English.

AB This study determined the disposition of irinotecan hydrochloride trihydrate (CPT-11) after i.v. infusion of 125 mg/m(2) (100 microCi) [(14)C]CPT-11 in eight patients with solid **tumors**. Mean +/- S.D. recovery of radioactivity in **urine** and feces was 95.8 +/- 2.7% (range 92.2-100.3%, n = 7) of dose. Radioactivity in blood, plasma, **urine**, and feces was determined for at least 168 h after dosing. Fecal excretion accounted for 63.7 +/- 6.8 (range 54.2-74.9%, n = 7) of dose, whereas urinary excretion accounted for 32.1 +/- 6.9% (range 21.7-43.8%; n = 7) of dose. One patient with a biliary T-tube excreted 30.1% of dose in bile, 14.2% in feces, and 48.2% in **urine**. Quantitative radiometric HPLC revealed that CPT-11 was the major excretion product in **urine**, bile, and feces. Aminopentane carboxylic acid (**APC**) and SN-38 glucuronide (SN-38G) were the most significant metabolites in **urine** and bile, whereas SN-38 and NPC, a primary amine metabolite, were relatively minor excretion products. SN-38 and **APC** were the most significant metabolites in feces. The relatively higher amount of SN-38 in feces compared with bile is presumably due to hydrolysis of SN-38G to SN-38 by enteric bacterial beta-glucuronidases. There was close correspondence between quantitative fluorescence HPLC and mass balance findings. CPT-11 was the major circulating component in plasma (55% of the mean radiochemical area under the curve), and CPT-11, SN-38, SN-38G, and **APC** accounted for 93% of the mean radiochemical AUC. These results show that the parent drug and its three major metabolites account for virtually all CPT-11 disposition, with fecal excretion representing the major elimination pathway.

L39 ANSWER 28 OF 50 CAPLUS COPYRIGHT 2002 ACS

2000:446256 Document No. 133:147798 Protein C inhibitor (PAI-3): structure and multi-function. Suzuki, K. (Department of Molecular Pathobiology, Mie University School of Medicine, Tsu-city, 514-8507, Japan). Fibrinolysis Proteolysis, 14(2/3), 133-145 (English) 2000. CODEN: FBPRFP. ISSN: 1369-0191. Publisher: Harcourt Publishers Ltd..

AB A review, with 99 refs. Protein C inhibitor (PCI) is a member of the serine protease inhibitor (serpin) family, which was initially found to be an inhibitor of activated protein C (**APC**) and later a potent inhibitor of the thrombin-thrombomodulin complex, suggesting that PCI plays a pivotal role in the regulation of the anticoagulant protein C pathway in human plasma. PCI is also known as a plasminogen activator inhibitor-3 (PAI-3), since this serpin was found in **urine** forming a complex with urokinase type-plasminogen activator (uPA). Human PCI also inhibits several other serine proteases involved in blood coagulation and fibrinolysis. Precursor proteins of PCI deduced from human, rhesus monkey, bovine, rabbit, rats and mouse cDNAs have sequence homol. 62-93%. Human PCI gene is located in a region involving genes of related serpins in chromosome 14q32.1. As regulatory mechanism of PCI gene expression, Sp1- and AP2-binding sites in the 5'-flanking region are the promoter and the enhancer, resp. PCI mRNA is expressed in many

organs, such as liver, kidney, spleen, pancreas, and reproductive organs (including testis, prostate, seminal vesicles and ovary in humans) and also in the liver and reproductive organs in bovines and rabbits; though in rats and mice only in the reproductive organs. PCI appears to play a role in the regulation of fertilization, presumably by inhibiting prostate specific antigen and acrosin in the male reproductive organs or by inhibiting protease(s) in the ovaries. In addn. to the roles of PCI in coagulation, fibrinolysis and fertilization, human PCI is also suggested to regulate wound healing and renal tumor metastasis by inhibiting hepatocyte growth factor activator and uPA, resp. Thus, PCI is a unique multi-functional serpin member playing several roles depending on species and organ tissues.

L39 ANSWER 29 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2000058772 EMBASE [Retroperitoneal desmoid tumour with renal failure in a patient with familial adenomatous polyposis]. RETROPERITONEALER DESMOIDTUMOR MIT NIERENINSUFFIZIENZ BEI FAMILIARER ADENOMATOSER POLYPOSIS. Bruckl W.M.; Wein A.; Riedel C.; Wiest G.H.; Hohenberger W.; Hahn E.G.. Dr. W.M. Bruckl, Medizinische Klinik I mit Poliklinik, F.-Alexander-Univ. Erlangen-Nurnberg, Krankenhausstrasse 12, 91054 Erlangen, Germany. wolfgang.brueckl@med1.med.uni-erlangen.de. Deutsche Medizinische Wochenschrift 125/4 (81-84) 28 Jan 2000. Refs: 21.

ISSN: 0012-0472. CODEN: DMWOAX. Pub. Country: Germany. Language: German. Summary Language: English; German.

AB History and findings: A 39-year-old man was hospitalized because of continually rising urinary creatinine and blood urea nitrogen concentration. He was known to have familial adenomatous polyposis (FAP), first diagnosed 18 years previously and re-Physical examination was unremarkable except for pain on percussion over both kidney regions. There was a well-healed laparotomy scar. Investigations: Ultrasound revealed chronic bilateral obstructive renal disease, grade II-III, and computed tomography showed a conglomerate retroperitoneal tumour with obstruction of both ureters at the level of the lower pelvis. This tumour had first been noted first 3 years after the colectomy when the patient complained of abdominal pain. It had been identified histologically as a nonresectable retroperitoneal desmoid tumour. Treatment and course: An external fistula was made, relieving the renal retention. To suppress growth of the desmoid tumour Sulindac, a nonsteroid anti-inflammatory drug, was administered. Genetic molecular analysis revealed a germ line defect in codon 1690 of the APC gene. It is intended to examine other members of the family for the presence of this defect. Conclusion: Desmoid tumours are more common in persons with FAP and are among the most frequent extracolonic causes of their death. Treatment options are critically analysed.

L39 ANSWER 30 OF 50 MEDLINE DUPLICATE 8

2000172771 Document Number: 20172771. PubMed ID: 10707780. The role of high-dose chemotherapy in the treatment of multiple myeloma: a controversy. Kyle R A. (Mayo Clinic, Rochester, MN, USA.) ANNALS OF ONCOLOGY, (2000) 11 Suppl 1 55-8. Ref: 19. Journal code: AYE; 9007735. ISSN: 0923-7534. Pub. country: Netherlands. Language: English.

AB BACKGROUND: Minimal criteria for the diagnosis of multiple myeloma are provided. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, primary systemic amyloidosis and metastatic carcinoma must be included in the differential diagnosis. Patients with multiple myeloma should not be treated unless they have an increasing M-protein in the serum or urine, development of anemia, hypercalcemia, renal insufficiency, lytic lesions, fractures or extra-medullary plasmacytomas. PATIENTS AND METHODS: This is a review of patients treated with chemotherapy, autologous stem-cell transplantation and allogeneic transplantation. RESULTS: Comparisons of melphalan and prednisone with a

variety of combinations of therapeutic agents produces a higher response rate than with melphalan and prednisone but no significant difference in overall survival. Autologous stem-cell transplantation produces a higher response rate and some prolongation of survival but is not curative. Allogeneic transplantation is associated with a mortality of 40% and is not curative. CONCLUSIONS: If the patient is younger than 70 years, the physician should consider the possibility of an autologous peripheral blood stem-cell transplant. Ideally, this should be done as part of a prospective study. Hematopoietic stem cells are damaged by alkylating agents so they must be collected before these agents are given. Autologous stem-cell transplantation does not produce a cure and most patients will relapse. The appropriate timing of an autologous stem-cell transplant has not been ascertained. Hopefully, better preparative regimens and the removal of contaminated **tumor** cells from the peripheral blood will make an autologous transplant more effective. Another major question is whether double (tandem) transplants are superior to a single autologous stem-cell transplant. A current French Myeloma Group Study randomized study should answer this question. Allogeneic transplantation for multiple myeloma must be made safer because the transplant-related mortality is 40%. The relapse of multiple myeloma following allogeneic transplant is a major problem and consequently the preparative regimens must be improved. The infusion of donor lymphocytes following relapse after an allogeneic transplant is useful. New approaches with immunologic aspects including the use of **dendritic cells** and vaccines are of potential importance for the future.

- L39 ANSWER 31 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 9
 1999:737073 Document No. 131:350237 Detection of antibody response to **tumor** markers for diagnostic and prognostic assessment of **cancer**. Robertson, John Forsyth Russell; Graves, Catherine Rosamund Louise; Price, Michael Rawling (The University of Nottingham, UK). PCT Int. Appl. WO 9958978 A2 19991118, 81 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1479 19990511. PRIORITY: GB 1998-10040 19980511.
- AB The authors disclose the detn. of the humoral immune response to circulating **tumor** marker proteins. The presence of complexes between the **tumor** marker antigens and any autoantibodies to the antigens present in a sample are detected and provide an assessment of the presence of **cancer**, its reoccurrence after treatment, and prognosis. In one example, antibodies to MUC-1, c-erbB2, c-myc, and p53 were shown to be indicative not only of **cancer** onset but also metastatic reoccurrence.

- L39 ANSWER 32 OF 50 CAPLUS COPYRIGHT 2002 ACS
 1999:468650 Document No. 131:99535 Multiplexed analysis of clinical specimens apparatus and methods. Chandler, Van S.; Fulton, Jerrold R.; Chandler, Mark B. (Luminex Corporation, USA). PCT Int. Appl. WO 9936564 A1 19990722, 301 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US918 19990115. PRIORITY: US 1998-8387 19980116.

AB A method for the multiplexed diagnostic and genetic anal. of enzymes, DNA fragments, antibodies, and other biomols. comprises the steps of constructing an appropriately labeled beadset, exposing the beadset to a clin. sample, and analyzing the combined sample/beadset by flow cytometry is disclosed. Flow cytometric measurements are used to classify, in real-time, beads within an exposed beadset and textual explanations, based on the accumulated data obtained during real-time anal., are generated for the user. The inventive technol. enables the simultaneous, and automated, detection and interpretation of multiple biomols. or DNA sequences in real-time while also reducing the cost of performing diagnostic and genetic assays.

L39 ANSWER 33 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 1999-430163 [36] WPIDS

CR 1998-216926 [19]

AB WO 9932634 A UPAB: 20011105

NOVELTY - Heat-killed *Mycobacterium vaccae*, or recombinant *M. vaccae* proteins, may be employed to activate T cells and natural killer (NK) cells, to stimulate the production of cytokines, to enhance the expression of co-stimulatory molecules on **dendritic cells** and monocytes, and to enhance dendritic cell maturation and function.

DETAILED DESCRIPTION - A polypeptide (I) comprising an immunogenic portion of an isolated *M. vaccae* antigen is new, and is selected from the 91, 136, 228, 231, 748, 221, 161, 541, 327, 134, 108, 348, 471, 722, 297, 670, 152, 331, 69, 268, 41, 111, 370, 159, 285, 243, 223, 187, 340 or 173 amino acid sequence given in the specification. Alternatively, (I) is at least 50%, 75% or 95% identical to one of these sequences, as measured by computer algorithm BLASTP. (I) is encoded by a polynucleotide (II), selected from the 273, 554, 808, 683, 1125, 666, 480, 1626, 985, 403, 336, 1111, 1420, 2172, 898, 2013, 520, 1071, 207, 898, 337, 1164, 650, 743 or 858 base pair sequence given in the specification. Alternatively, (II) is the complement of one of these sequences, or has a 99% probability of being the same sequence as measured by computer algorithm BLASTN.

INDEPENDENT CLAIMS are also included for the following:

- (1) an expression vector comprising (II);
- (2) a host cell, preferably *E. coli*, mycobacteria, insect, yeast or mammalian cells, transformed with the vector of (1);
- (3) a fusion protein comprising (I);
- (4) a pharmaceutical composition comprising (I) or (II) or the fusion protein of (3) and a physiologically acceptable carrier;
- (5) a vaccine comprising (I) or (II) or the fusion protein of (3) and a non-specific immune response amplifier;
- (6) a method for enhancing an immune response in a patient, comprising administering the pharmaceutical composition of (4) or the vaccine of (5);
- (7) a method for the treatment of a disorder in a patient, comprising administering the pharmaceutical composition of (4) or the vaccine of (5);
- (8) a method for the treatment of a disorder in a patient, comprising administering a composition comprising a component selected from:
 - (a) inactivated *M. vaccae* cells;
 - (b) delipidated and deglycolipidated *M. vaccae* cells depleted of mycolic acids;
 - (c) delipidated and deglycolipidated *M. vaccae* cells depleted of mycolic acid and arabinogalactan; and *M. vaccae* culture filtrate;
- (9) a method for enhancing a non-specific immune response to an antigen, comprising administering a polypeptide comprising an immunogenic portion of a *M. vaccae* antigen selected from:
 - (a) the 376 or 223 amino acid sequence given in the specification; or
 - (b) sequences at least 80% identical to these, as measured by computer algorithm BLASTP;
- (10) a method for detecting mycobacterial infection in a patient,

comprising contacting the dermal cells of the patient with (I) and detecting an immune response, e.g. induration, on the patients skin;

(11) a diagnostic kit comprising (I) and apparatus sufficient to contact the polypeptide with the dermal cells of a patient;

(12) a method for detecting mycobacterial infection in a biological sample, comprising contacting the sample with (I) and detecting the presence of antibodies that bind to the polypeptide. The polypeptides are optionally bound to a solid support;

(13) a method for detecting mycobacterial infection in a biological sample, comprising contacting the sample with a binding agent, e.g. a mono- or a polyclonal antibody, which is capable of binding to (I) and detecting this binding;

(14) a diagnostic kit comprising (I) (preferably immobilized on a solid support) and a detection reagent, e.g. a reporter group (which is especially a radioisotope, a fluorescent group, a luminescent group, an enzyme, biotin or dye particles) conjugated to a binding agent (which is especially an anti-immunoglobulin, Protein G, Protein A or lectin);

(15) a mono- or polyclonal antibody that binds to (I); and

(16) a method for enhancing a non-specific immune response to an antigen, comprising administering a composition comprising a component selected from:

(a) delipidated and deglycolipidated *M. vaccae* cells depleted of mycolic acids;

(b) delipidated and deglycolipidated *M. vaccae* cells depleted of mycolic acid and arabinogalactan.

ACTIVITY - Antiasthmatic; Antiinflammatory; Antipsoriatic; Cytostatic; Dermatological; Tuberculostatic.

MECHANISM OF ACTION - Vaccine.

USE - The compositions can be used for the treatment, prevention, and detection of disorders including infectious diseases (claimed), immune disorders (claimed) and cancer. In particular, the compounds and methods are used for treatment of diseases of the respiratory system (claimed), such as mycobacterial infections (claimed), asthma (claimed), allergies, tuberculosis, leprosy, sarcoidosis and lung cancers, and disorders of the skin (claimed) such as psoriasis (claimed), atopic dermatitis, eczema, allergic contact dermatitis, alopecia areata, and skin cancers such as basal carcinoma, squamous cell carcinoma and melanoma.

The products can also be used as vaccines or in immunotherapy.

ADVANTAGE - Of all the available therapies for treating cutaneous

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L39 ANSWER 33 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 1999-430163 [36] WPIDS

CR 1998-216926 [19]

AB WO 9932634 A UPAB: 20011105

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least 50%, 75% or 95% identical to one of these sequences, as measured by computer algorithm BLASTP. (I) is encoded by a polynucleotide (II), selected from the 273, 554, 808, 683, 1125, 666, 480, 1626, 985, 403, 336, 1111, 1420, 2172, 898, 2013, 520, 1071, 207, 898, 337, 1164, 650, 743 or 858 base pair sequence given in the specification. Alternatively, (II) is the complement of one of these sequences, or has a 99% probability of being the same sequence as measured by computer algorithm BLASTN.

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- (3) a fusion protein comprising (I);
- (4) a pharmaceutical composition comprising (I) or (II) or the fusion protein of (3) and a physiologically acceptable carrier;
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 - (c) delipidated and deglycolipidated *M. vaccae* cells depleted of mycolic acid and arabinogalactan; and
M. vaccae culture filtrate;
- (9) a method for enhancing a non-specific immune response to an antigen, comprising administering a polypeptide comprising an immunogenic portion of a *M. vaccae* antigen selected from:
 - (a) the 376 or 223 amino acid sequence given in the specification; or
 - (b) sequences at least 80% identical to these, as measured by computer algorithm BLASTP;
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- (11) a diagnostic kit comprising (I) and apparatus sufficient to contact the polypeptide with the dermal cells of a patient;
- (12) a method for detecting mycobacterial infection in a biological sample, comprising contacting the sample with (I) and detecting the presence of antibodies that bind to the polypeptide. The polypeptides are optionally bound to a solid support;
- (13) a method for detecting mycobacterial infection in a biological sample, comprising contacting the sample with a binding agent, e.g. a mono- or a polyclonal antibody, which is capable of binding to (I) and detecting this binding;
- (14) a diagnostic kit comprising (I) (preferably immobilized on a solid support) and a detection reagent, e.g. a reporter group (which is especially a radioisotope, a fluorescent group, a luminescent group, an enzyme, biotin or dye particles) conjugated to a binding agent (which is especially an anti-immunoglobulin, Protein G, Protein A or lectin);
- (15) a mono- or polyclonal antibody that binds to (I); and
- (16) a method for enhancing a non-specific immune response to an antigen, comprising administering a composition comprising a component selected from:
 - (a) delipidated and deglycolipidated *M. vaccae* cells depleted of mycolic acids;
 - (b) delipidated and deglycolipidated *M. vaccae* cells depleted of mycolic acid and arabinogalactan.

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The products can also be used as vaccines or in immunotherapy.

ADVANTAGE - Of all the available therapies for treating cutaneous lesions, only interferon possesses a specific antiviral mode of action, by reproducing the body's immune response to infection. However, Interferon treatment cannot eradicate viruses. Interferon treatment is also associated with systemic adverse effects, and requires multiple injections, at a significant economic cost. Use of *M. vaccae* to immunize individuals overcomes these problems.

Dwg.0/13

L39 ANSWER 34 OF 50 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 1999-264099 [22] WPIDS

AB WO 9918437 A UPAB: 19990609

NOVELTY - Detectable compound comprises a heterobifunctionalized chromophore in which one functionality on the chromophore is capable of coupling with a signal-enhancing agent or blocking agent and the other functionality is capable of coupling with a member of a specific binding pair.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for detectable complexes comprising the detectable compound described and a signal-enhancing agent, blocking agent and/or a member of a specific binding pair.

ACTIVITY - None given.

MECHANISM OF ACTION - Normal human blood (50 μ l) containing EDTA was incubated with 38 ng (A) test compound CD3-Cyc5.5-PerCP (Cy5.5 buried), (B) CD3-Cyc5.5-PerCP (Cy5.5 exposed) or (C) CD3-PerCP for 30 minutes at 25 deg. C. Lysing solution (1 ml, FACS Lysing Solution) was added and, after incubation for 10 minutes at 25 deg. C, the samples were centrifuged (10 minutes; 200xg). The pellet was resuspended in phosphate-buffered saline (0.5 ml)/bovine serum albumin (0.5%) and analyzed with a FACScan (TM)-type flowcytometer. Lymphocytes stained with test compound (A) were approximately 5 times brighter than lymphocytes stained with (C). Importantly fluor-specific binding of monocytes was significantly (10-fold) lower using test compound (A) compared with (B). In addition, the baseline gap between the monocyte peak and lymphocytes stained with test compound (A) was significantly greater than when stained with either (B) or (C) (over 1 log versus 90.1 and 0.9 logs, respectively) demonstrating that different cell populations can be more accurately assessed using the test compound. The results demonstrated the superior features of the test complex.

USE - The detectable compound is used in fluorescence assays as a reagent (claimed), used to label materials such as proteins or cells and to label antibodies for use as immunological agents in e.g. fluorescent-activated cell sorting or analysis, immunoassays and immunostaining as well as detection of tumors in vivo. The compound maybe used to label protein ligands such as growth factors or cytokines to study ligand-receptor interactions for research or clinical purposes, or used to label non-protein molecules such as morphine and phencyclidine for competitive immunoassays to detect drug levels in urine. The detectable compound may also be used to label nucleotides or oligonucleotides for research and clinical applications

including DNA and RNA hybridization-based diagnostic methods, DNA and RNA sequencing, restriction fragment mapping and fluorescence in situ hybridization.

ADVANTAGE - Heterobifunctionalized chromophore have reduced chromophore-mediated undesirable binding (claimed) ensuring no quenching of the chromophore signal. The chromophore is sterically hindered from interacting non-specifically with substances present in test systems and can be used as a crosslinker with little or no loss of detectable signal. Prior-art problems are overcome with dimness, photobleaching, signal spillover into neighboring detection channels, instability and non-specific binding to irrelevant or inappropriate components of the analytical system.

Dwg.0/3

L39 ANSWER 35 OF 50 MEDLINE

1999342987 Document Number: 99342987. PubMed ID: 10416598. Transforming growth factor beta1 suppresses nonmetastatic colon **cancer** at an early stage of tumorigenesis. Engle S J; Hoving J B; Boivin G P; Ormsby I; Gartside P S; Doetschman T. (Department of Molecular Genetics, Biochemistry, and Microbiology, University of Cincinnati, Ohio 45267, USA.) CANCER RESEARCH, (1999 Jul 15) 59 (14) 3379-86. Journal code: CNF; 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The transforming growth factor beta (TGF-beta) pathway is known to play an important role in both human and **urine** colon **cancer**. However, the staging, ligand specificity, and mechanism underlying the **tumor** suppressive activity of this pathway are unknown. We developed a mouse model for colon **cancer** that identifies an early role for TGF-beta1 in **tumor** suppression and implicates TGF-beta2 or TGF-beta3 in the prevention of metastasis. Analysis of the development of colon **cancer** in TGF-beta1 knockout mice pinpoints the defect to the hyperplasia/adenoma transition and reveals that the mechanism involves an inability to maintain epithelial tissue organization and not a loss of growth control, increased inflammatory activity, or increased genetic instability. These mice provide a unique opportunity to investigate the specific role of TGF-beta1 at this critical transition in the development of colon **cancer**.

L39 ANSWER 36 OF 50 MEDLINE DUPLICATE 10

2000062089 Document Number: 20062089. PubMed ID: 10596953. Enrichment of mutant alleles by chromatographic removal of wild type alleles: a new principle for the detection of alleles with unknown point mutations at excess of wild type alleles. Nollau P; Fischer C; Tschentscher P; Wagener C. (Abteilung für Klinische Chemie, Medizinische Klinik, Universitätskrankenhaus Eppendorf, Hamburg, Germany.) CLINICAL CHEMISTRY AND LABORATORY MEDICINE, (1999 Sep) 37 (9) 877-81. Journal code: CZ8; 9806306. ISSN: 1434-6621. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB In human carcinomas, mutations that alter tumour genes such as the KRAS, P53, or **APC** genes, are mostly point mutations. The detection of mutant alleles of tumour genes in specimens such as **urine**, pancreatic juice, sputum, and stool holds great promise for an early diagnosis of **cancer**. In addition, the detection of mutant tumour genes in tissue samples, such as lymph nodes or resection margins, may allow a sensitive diagnosis of residual malignant disease. However, the reliable detection of mutant alleles in excess of wild type alleles remains an unresolved analytical problem when the mutations are not known a priori. In the present communication, a new approach is described which makes possible the detection of unknown point mutations in tumour genes at excess of wild type alleles. The method is based on the removal of wild type alleles by hybridisation to immobilised complementary oligonucleotides. Using this approach, an enrichment of mutant KRAS, P53 and **APC** alleles of one mutant in up to 10(3) normal alleles has

been achieved. Parallel miniaturised separation units with oligonucleotides complementary to defined sequences of a wild type allele should allow the detection of unknown point mutations as well as small insertions or deletions which occur in the sequence range covered by the oligonucleotides.

L39 ANSWER 37 OF 50 CAPLUS COPYRIGHT 2002 ACS

1998:774860 Document No. 130:123652 FLT3-ligand administration inhibits liver metastases: role of NK cells. Peron, Jean-Marie; Esche, Clements; Subbotin, Vladimir M.; Maliszewski, Charles; Lotze, Michael T.; Shurin, Michael R. (Biol. Therapeutics Program, Univ. Pittsburgh Cancer Inst., Pittsburgh, PA, 15213, USA). J. Immunol., 161(11), 6164-6170 (English) 1998. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB FLT3-ligand (FL) is a recently described cytokine that stimulates the proliferation and differentiation of hematopoietic progenitors both in vivo and in vitro and, when administered to mice, induces an accumulation of **dendritic cells** (DC) in different lymphoid and nonlymphoid organs and tissues, including the liver. We have studied the antitumor effect of FL administered alone or in combination with IL-12 in a day 3 murine liver metastasis model. FL significantly reduced the no. of hepatic metastases (36.00+-.11.00 vs. 92.00+-.10.19 in control group). Histol. evaluation of the livers revealed that FL induced a significant infiltration of the **tumor** border by lymphocytes and DC assocd. with increased no. of apoptotic figures. Immunochem. anal. demonstrated that FL significantly enhanced the no. of DC in the liver parenchyma and within the liver metastases, as well as the no. of CD4+ and CD8+ T lymphocytes. These data support the suggestion that DC may be directly involved in the antitumor effect of FL. Interestingly, the antitumor effect of FL was greatly reduced by the NK depletion. Combination of FL and IL-12 resulted in greater antitumor efficacy than these cytokines alone. In summary, we have shown that FL has significant antitumor effect on preexisting murine C3 liver **tumors** that is mediated by NK cells. We have also demonstrated that the FL/IL-12 combination has an enhanced antitumor activity in the same **urine tumor** model.

L39 ANSWER 38 OF 50 MEDLINE DUPLICATE 11

1999045203 Document Number: 99045203. PubMed ID: 9829738. Irinotecan (CPT-11) metabolism and disposition in **cancer** patients. Sparreboom A; de Jonge M J; de Bruijn P; Brouwer E; Nooter K; Loos W J; van Alphen R J; Mathijssen R H; Stoter G; Verweij J. (Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, The Netherlands.. sparreboom@onch.azr.nl) . CLINICAL CANCER RESEARCH, (1998 Nov) 4 (11) 2747-54. Journal code: C2H; 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.

AB The objective of this study was to determine the metabolic fate and disposition of the antitumor camptothecine derivative irinotecan (CPT-11). Ten patients with histological proof of malignant solid **tumor** received 200 mg/m2 CPT-11 as a 90-min i.v. infusion, followed by a 1.5-h i.v. infusion of cisplatin (60 or 80 mg/m2). Plasma, **urine**, and feces were collected for 56 h and analyzed by a specific reversed-phase high-performance liquid chromatographic assay for the parent drug and all four metabolites positively identified to date: SN-38; its beta-glucuronide conjugate, SN-38 beta-glucuronide (SN-38G); 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecine (**APC**); and 7-ethyl-10-[4-N-(1-piperidino)-1-amino]-carbonyloxycamptothecine (**NPC**). A three-exponential decline was observed in plasma for all compounds, with a clear predominance of the parent drug [25.6+/-5.71 microM x h (CPT-11) versus 15.8+/-3.51 microM x h (total metabolites)]. Total urinary excretion was 28.1+/-10.6% of the dose, with unchanged CPT-11 and SN-38G as the main

excretion products. Whereas renal clearance of SN-38 was only a minor route of drug elimination, fecal concentrations of this compound were unexpectedly high (on average, 2.45% of the dose), suggestive of intestinal hydrolysis of SN-38G by bacterial beta-glucuronidase. CPT-11 and the other metabolites could also be identified from fecal extracts, with a very minor contribution overall of the cytochrome P-450-mediated compounds 7-ethyl-10-[4-N-(1-piperidino)-1-amino]-carbonyloxycamptothecin and 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin. Surprisingly, fecal excretion accounted for only 24.4+/-13.3% of the dose, leading to a total excretion of approximately 52%. These data indicate that half of the dose in **urine** and feces may constitute some further unknown nonextractable or nonfluorescent metabolites. The findings from this study should be of importance as a guide to further therapeutic evaluation of this drug.

L39 ANSWER 39 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 12

1998:744016 Document No. 130:162577 Pharmacology of irinotecan. Robert, Jacques; Rivory, Laurent (Institut Bergonie and Universite Victor Segalen Bordeaux 2, Bordeaux, 33076, Fr.). Drugs Today, 34(9), 777-803 (English) 1998. CODEN: MDACAP. ISSN: 0025-7656. Publisher: Prous Science.

AB A review with 187 refs. Irinotecan (CPT-11) is a semisynthetic deriv. of camptothecin, an alkaloid extd. from the Chinese plant *Camptotheca acuminata*. It bears a bispiperidine moiety and was selected for its water soly. and promising preclin. antitumor activity in in vitro and in vivo models. The target of drugs of the camptothecin family is DNA topoisomerase I, a nuclear enzyme involved in the relaxation of the DNA double helix required for replication and transcription activities. Such drugs stabilize the enzyme-DNA complex and prevent the religation of the single-strand breaks created by the enzyme, which are converted to double-strand breaks upon the collision with a replication fork during the S-phase. Resistance to irinotecan appears not to be mediated by P-glycoprotein, but by qual. and/or quant. alterations of its target, topoisomerase I, or by alterations occurring downstream from this interaction. As with all camptothecin derivs., irinotecan contains a lactone ring that can be spontaneously and reversibly hydrolyzed to a carboxylate open ring form, which predominates at neutral and alk. pH and is inactive on topoisomerase I-DNA complexes. Irinotecan is, in fact, much less active than its metabolite SN-38 and is generally considered as a prodrug of this compd. The carboxylesterase which carries out this conversion is preferentially active on the lactone form of irinotecan and directly generates the lactone form of SN-38, which may explain the superiority of irinotecan over SN-38 in vivo. Further metab. of SN-38 to a .beta.-glucuronide conjugate is a major pathway of detoxification and plays an important role in detg. irinotecan toxicity in the clin. setting. Other metabolic pathways of irinotecan involve oxidns. occurring on the bispiperidine rings, which are carried out by cytochrome P 450. Irinotecan has shown an important activity in advanced and metastatic colorectal carcinoma and is now used for this indication in several countries, with 2 different recommended schedules: weekly administration of 125 mg/m² with a 2-wk drug-free interval every 4 administrations, or 3-weekly administration of 350 mg/m², a dose that can be increased to 500 mg/m² with the support of antidiarrheal compds. Other possible indications of irinotecan include lung and cervix **cancer**, which are presently under investigation. The dose-limiting toxicity of irinotecan is mainly diarrhea, which occurs 7-10 days after treatment and can be life-threatening when assocd. with neutropenia, another frequent side effect. High-dose loperamide has shown good efficacy for treating this diarrhea and has allowed an increase in irinotecan doses tolerated by patients. The pharmacokinetics of irinotecan are characterized by a 2- or 3-compartment decay, with a terminal half-life of about 10 h, a total vol. of distribution of 150 L/m² and a total plasma clearance of 15 L/h/m². The AUC of SN-38 is only a small fraction of that of irinotecan (2-4%) and

SN-38 is eliminated from plasma with a half-life of about 12 h. SN-38 glucuronide is present in plasma at higher concns. than free SN-38 and is eliminated at the same rate. **APC**, produced by the action of cytochrome P 450, isoenzyme 3A4, is present in plasma at concns. close to those of irinotecan itself. Only a small fraction of irinotecan and its metabolites is eliminated in **urine**, and a higher proportion in the bile, with an enterohepatic cycle of SN-38 glucuronide and SN-38. Significant relationships have been established between the AUCs of both irinotecan and SN-38 and hematol. and intestinal toxicities, suggesting a potential use for monitoring this drug.

L39 ANSWER 40 OF 50 MEDLINE DUPLICATE 13
 1998361711 Document Number: 98361711. PubMed ID: 9698245. Liquid chromatographic determination of irinotecan and three major metabolites in human plasma, **urine** and feces. Sparreboom A; de Bruijn P; de Jonge M J; Loos W J; Stoter G; Verweij J; Nooter K. (Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, The Netherlands.) JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL SCIENCES AND APPLICATIONS, (1998 Aug 7) 712 (1-2) 225-35. Journal code: CXN; 9714109. ISSN: 1387-2273. Pub. country: Netherlands. Language: English.

AB A new simple reversed-phase high-performance liquid chromatographic method was developed for the determination of irinotecan (CPT-11) and three metabolites in human plasma, **urine** and feces homogenate. The metabolites of interest were 7-ethyl-10-hydroxycamptothecin (SN-38), its beta-glucuronide derivative (SN-38G) and 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (RPR 121056A; also referred to as **APC**). Sample pretreatment from the various biological matrices involved a rapid protein precipitation with simultaneous solvent extraction of 250-microl aliquots of sample with 500 microl of methanol-5% (w/v) aqueous perchloric acid (1:1, v/v). Separation of the compounds was achieved on an analytical column packed with Hypersil ODS material (100X4.6 mm I.D., 5 microm), and isocratic elution with a mixture of methanol-0.1 M ammonium acetate containing 10 mM tetrabutylammonium sulphate (30:70, v/v), pH 5.3 (hydrochloric acid). The column effluent was monitored at excitation and emission wavelengths of 355 and 515 nm, respectively. Results from a 4-day validation study indicated that this single-run determination allows for simple, simultaneous and rapid quantitation and identification of all analytes with excellent reliability. The described procedure permits the analysis of patient samples, and will be implemented in future studies to investigate the complete metabolic fate and disposition of CPT-11 in **cancer** patients.

L39 ANSWER 41 OF 50 MEDLINE
 1998421897 Document Number: 98421897. PubMed ID: 9751277. The effect of soy isoflavones on the development of intestinal neoplasia in ApcMin mouse. Sorensen I K; Kristiansen E; Mortensen A; Nicolaisen G M; Wijnands J A; van Kranen H J; van Kreijl C F. (Danish Veterinary and Food Administration, Institute of Food Safety and Toxicology, Soborg.. iks@vfd.dk) . CANCER LETTERS, (1998 Aug 14) 130 (1-2) 217-25. Journal code: CMX; 7600053. ISSN: 0304-3835. Pub. country: Ireland. Language: English.

AB Data from epidemiological studies suggest that isoflavones in soy may have a protective effect on the development of colon **cancer** in humans. Therefore, we have investigated whether soy isoflavones will inhibit intestinal tumour development in **Apc**(Min) mice. The mice were fed a Western-type high risk diet (high fat, low fibre and calcium) containing two different isolates of soy protein as a protein source. For the control and test groups this resulted in the administration of about 16 and 475 mg of total isoflavones per kg diet, respectively. As a positive control. a third group of mice was administered a low isoflavone

diet supplemented with 300 ppm sulindac. No significant differences in the incidence, multiplicity, size and distribution of intestinal tumours were observed between Min mice fed low and high isoflavone-containing diets. However, a clear reduction in the number of small intestinal tumours was observed for the sulindac diet. Thus, in contrast to epidemiological studies, our results demonstrate that high amounts of soy isoflavones present in a Western-type high risk diet do not protect against intestinal tumour development in a relevant animal model such as the Min mice.

L39 ANSWER 42 OF 50 CAPLUS COPYRIGHT 2002 ACS

1998:723545 Document No. 130:48593 Metabolism and genotoxicity of food-derived heterocyclic amines. Gooderham, Nigel J.; Lynch, Anthony M.; Yadollahi-Farsani, Masoud; Murray, Stephen; Boobis, Alan R.; Davies, Donald S. (Clinical Pharmacology, Division of Medicine, Imperial College School of Medicine, Hammersmith Hospital, London, W12 0NN, UK). Biomed. Health Res., 25(Drug Metabolism: Towards the Next Millennium), 127-136 (English) 1998. CODEN: BIHREN. ISSN: 0929-6743. Publisher: IOS Press.

AB When meat is cooked, potent pro-genotoxic heterocyclic amines are formed at levels of ppb. The three heterocyclic amines most commonly found in cooked red meat are 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). After consumption of a fried beef meal, these amines are readily absorbed, extensively metabolized and rapidly excreted in both **urine** and feces. Both MeIQx and PhIP are efficiently converted to their N-hydroxy derivs., the major hepatic oxidative metabolites formed by CYP1A2 in man whereas animals also produce ring hydroxylated derivs. These N-hydroxy compds. are direct acting bacterial mutagens whereas the ring hydroxylated species are detoxication products. Although MeIQx is a very powerful bacterial mutagen, PhIP is a better mammalian cell mutagen and it preferentially causes genotoxic damage at guanine producing a characteristic pattern ("fingerprint") of mutations. Since evidence of this "fingerprint" has been detected in the **Apc** gene in PhIP induced colonic **tumors** in rats, we believe the PhIP mutational "fingerprint" could be diagnostic of its involvement in mutation.

L39 ANSWER 43 OF 50 MEDLINE DUPLICATE 14

1999130871 Document Number: 99130871. PubMed ID: 9932079. [Irinotecan pharmacokinetics]. Pharmacocinetique de l'irinotecan. Chabot G G; Robert J; Lokiec F; Canal P. (Hopital Saint-Louis, Centre Hayem, Inserm U, Paris.) BULLETIN DU CANCER, (1998 Dec) Spec No 11-20. Ref: 116. Journal code: BDZ; 0072416. ISSN: 0007-4551. Pub. country: France. Language: French.

AB The clinical pharmacokinetics of irinotecan (CPT11) can be described by a 2 or 3 compartment model, a mean terminal half-life of 12 hours, a volume of distribution at steady state of 168 l/m2 and a total body clearance of 15 l/m2/h. Irinotecan is 65% bound to plasma proteins. The areas under the plasma concentration-time curve (AUC) of both irinotecan and active metabolite SN38 increase proportionally to the administered dose, although interpatient variability is important. SN38 levels achieved in humans are about 100-fold lower than corresponding irinotecan levels, but these concentrations are important since SN38 is 100- to 1,000-fold more cytotoxic than the parent compound. SN38 is 95% bound to plasma proteins. SN38 plasma decay follows closely that of the parent compound. Irinotecan is extensively metabolized in the liver. The bipiperidinocarbonyloxy group of irinotecan is first removed by a carboxyesterase to yield the corresponding carboxylic acid and SN38. This metabolite can be converted into SN38 glucuronide by UDP-glucuronyltransferase (1.1 isoform). A recently identified metabolite is the 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxy-camptothecin (**APC**), which is formed by the action of cytochrome P450 3A4. Numerous other unidentified metabolites are detected in bile and **urine**. The mean 24 h irinotecan urinary excretion represents 17-25% of the administered dose,

whereas SN38 and its glucuronide recovery in **urine** is minimal (0.5 and 6%, respectively). Irinotecan and SN38 pharmacokinetics are not influenced by prior exposure to the parent drug. Irinotecan and SN38 AUCs correlate significantly with leuko-neutropenia and sometimes with the intensity of diarrhea. Increased bilirubin levels appear to influence irinotecan total body clearance. The observation that most **tumor** responses were seen at the highest doses administered in phase I trials suggest a dose-response relationship with this drug. These pharmacokinetic-pharmacodynamic relationships may prove useful for a better clinical management of this drug aimed at a better control of toxicities and a better prediction of **tumor** response for the benefit of the individual patient.

- L39 ANSWER 44 OF 50 MEDLINE DUPLICATE 15
1998001853 Document Number: 98001853. PubMed ID: 9342501. Clinical pharmacokinetics of irinotecan. Chabot G G. (Pharmacology Laboratory (URA 147 CNRS), Gustave-Roussy Institute, Villejuif, France.. gchabot@igr.fr) . CLINICAL PHARMACOKINETICS, (1997 Oct) 33 (4) 245-59. Ref: 114. Journal code: DG5; 7606849. ISSN: 0312-5963. Pub. country: New Zealand. Language: English.
- AB This article reviews the clinical pharmacokinetics of a water-soluble analogue of camptothecin, irinotecan [CPT-11 or 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin]. Irinotecan, and its more potent metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin), interfere with mammalian DNA topoisomerase I and **cancer** cell death appears to result from DNA strand breaks caused by the formation of cleavable complexes. The main clinical adverse effects of irinotecan therapy are neutropenia and diarrhoea. Irinotecan has shown activity in leukaemia, lymphoma and the following **cancer** sites: colorectum, lung, ovary, cervix, pancreas, stomach and breast. Following the intravenous administration of irinotecan at 100 to 350 mg/m², mean maximum irinotecan plasma concentrations are within the 1 to 10 mg/L range. Plasma concentrations can be described using a 2- or 3-compartment model with a mean terminal half-life ranging from 5 to 27 hours. The volume of distribution at steady-state (V_{ss}) ranges from 136 to 255 L/m², and the total body clearance is 8 to 21 L/h/m². Irinotecan is 65% bound to plasma proteins. The areas under the plasma concentration-time curve (AUC) of both irinotecan and SN-38 increase proportionally to the administered dose, although interpatient variability is important. SN-38 levels achieved in humans are about 100-fold lower than corresponding irinotecan concentrations, but these concentrations are potentially important as SN-38 is 100- to 1000-fold more cytotoxic than the parent compound. SN-38 is 95% bound to plasma proteins. Maximum concentrations of SN-38 are reached about 1 hour after the beginning of a short intravenous infusion. SN-38 plasma decay follows closely that of the parent compound with an apparent terminal half-life ranging from 6 to 30 hours. In human plasma at equilibrium, the irinotecan lactone form accounts for 25 to 30% of the total and SN-38 lactone for 50 to 64%. Irinotecan is extensively metabolised in the liver. The bipiperidinocarbonyloxy group of irinotecan is first removed by hydrolysis to yield the corresponding carboxylic acid and SN-38 by carboxyesterase. SN-38 can be converted into SN-38 glucuronide by hepatic UDP-glucuronyltransferase. Another recently identified metabolite is 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxy-camptothecin (APC). This metabolite is a weak inhibitor of KB cell growth and a poor inducer of topoisomerase I DNA-cleavable complexes (100-fold less potent than SN-38). Numerous other unidentified metabolites have been detected in bile and **urine**. The mean 24-hour irinotecan urinary excretion represents 17 to 25% of the administered dose. Recovery of SN-38 and its glucuronide in **urine** is low and represents 1 to 3% of the irinotecan dose. Cumulative biliary excretion is 25% for irinotecan, 2% for SN-38 glucuronide and about 1% for SN-38. The pharmacokinetics of irinotecan and

SN-38 are not influenced by prior exposure to the parent drug. The AUC of irinotecan and SN-38 correlate significantly with leuco-neutropenia and sometimes with the intensity of diarrhoea. Certain hepatic function parameters have been correlated negatively with irinotecan total body clearance. It was noted that most tumour responses were observed at the highest doses administered in phase I trials, which indicates a dose-response relationship with this drug. In the future, these pharmacokinetic-pharmacodynamic relationships will undoubtedly prove useful in minimising the toxicity and maximise the likelihood of tumour response in patients.

L39 ANSWER 45 OF 50 CAPLUS COPYRIGHT 2002 ACS

1997:637313 Document No. 127:326900 FLT3 ligand induces the generation of functionally active **dendritic cells** in mice. Shurin, Michael R.; Pandharipande, Pratik P.; Zorina, Tatiana D.; Haluszczak, Catherine; Subbotin, Vladimir M.; Hunter, Oriana; Brumfield, Anne; Storkus, Walter J.; Maraskovsky, Eugene; Lotze, Michael T. (Biologic Therapeutics Program, University Pittsburgh Cancer Institute, Pittsburgh, PA, 15213, USA). Cell. Immunol., 179(2), 174-184 (English) 1997. CODEN: CLIMB8. ISSN: 0008-8749. Publisher: Academic.

AB FLT3 ligand (FL) is a recently described hematopoietic growth factor that stimulates the proliferation and differentiation of hematopoietic progenitors. The authors have investigated the effect of FL on murine hematopoiesis and dendritic cell (DC) generation and accumulation in lymphoid tissues and liver in vivo and in vitro, evaluating the morphol., phenotypic, and functional characteristics of these DC. They obsd. extramedullary hematopoiesis in the mouse spleen with all lineages of hematopoietic cells represented after the administration of FL. Injection of FL results in a time-dependent and reversible accumulation of DC in the spleen, bone marrow, lymph nodes, and liver. Both flow cytometry and immunohistochem. revealed a significant accumulation of DC in these tissues. Results of mixed leukocyte reaction suggested that these cells, isolated from **urine** bone marrow or spleen, were active as **antigen presenting cells**. Furthermore, cultivation of splenic and marrow cells with GM-CSF and IL-4 gave rise to large nos. of functionally active mature DC. Thus, the results of this study suggest that FL is a promising growth factor that stimulates the generation of large no. of DC and may be a useful cytokine for the immunotherapy of **cancer**.

L39 ANSWER 46 OF 50 MEDLINE DUPLICATE 16

96374990 Document Number: 96374990. PubMed ID: 8781372. Human exposure to carcinogenic heterocyclic amines and their mutational fingerprints in experimental animals. Nagao M; Wakabayashi K; Ushijima T; Toyota M; Totsuka Y; Sugimura T. (Carcinogenesis Division, National Cancer Center Research Institute, Tokyo, Japan.. mnagao@gan.ncc.go.jp) . ENVIRONMENTAL HEALTH PERSPECTIVES, (1996 May) 104 Suppl 3 497-501. Ref: 31. Journal code: EIO; 0330411. ISSN: 0091-6765. Pub. country: United States. Language: English.

AB Heterocyclic amines (HCAs) are mutagens/carcinogens to which humans are exposed on almost a daily basis. 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhlP) is the most abundant of the various carcinogenic HCAs (present at a level of 0.56 to 69.2 ng/g of cooked meat or fish), with 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) following it at 0.64 to 6.44 ng/g. HCAs have been found in the **urine** of healthy people who consume ordinary diets, while patients receiving parenteral alimentation lack, for example, PhlP and MeIQx in their **urine**. Based on the concentrations of PhlP and MeIQx in **urine** samples from 10 healthy volunteers, daily intake of MeIQx in Japanese was calculated to be 0.3 to 3.9 micrograms/person, while that of PhlP was 0.005 to 0 micrograms. The Japanese consume more MeIQx than Americans, whereas Japanese intake of PhlP was about one-third that of Americans.

MelQx-DNA adducts have also detected in Japanese Kidney, colon, and rectum samples using the 32P-postlabeling method followed by identification using high-performance liquid chromatography (HPLC) analysis; the levels were 0.18, 1.8, and 1.4 per 10(9) nucleotides, respectively. In addition, we elucidated the mutational fingerprints of Phlp by analyzing **Apc** mutations in rat colon **cancers** induced by this carcinogen. Four of eight **tumors** had a total of five mutations in the **Apc** gene, four of which featured a guanine deletion from 5'-GTGGGAT-3' sequences. This specific mutation spectrum may be used as a fingerprint of Phlp in evaluating its risk potential for human colon carcinogenesis. Mutations were not found in similar 2-amino-3-methylimidazo[4,5-f]quinoline-induced colon lesions. Microsatellite instability was detected in both colon and mammary **tumors** induced by Phlp. The mechanisms involved in this development of microsatellite instability in Phlp. The mechanisms involved in this development of microsatellite instability in Phlp-induced **cancers** remain to be elucidated.

L39 ANSWER 47 OF 50 CAPLUS COPYRIGHT 2002 ACS

1993:78665 Document No. 118:78665 Inherited and somatic mutations of the **APC** gene associated with colorectal **cancer** of humans. Kinzler, Kenneth W.; Vogelstein, Bert; Anand, Rakesh; Hedge, Philip John; Markham, Alexander Fred; Albertsen, Hans; Carlson, Mary L.; Groden, Joanna L.; Joslyn, Geoff; et al. (Johns Hopkins University, USA; Imperial Chemical Industries PLC; University of Utah; Cancer Institute). PCT Int. Appl. WO 9213103 A1 19920806, 138 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US376 19920116. PRIORITY: GB 1991-963 19910116; US 1991-741940 19910808.

AB A human gene that shows inherited and somatic mutations assocd. with colorectal **cancer** is cloned and characterized. The gene and its product are useful as markers in the diagnosis and prognosis of the disease. A series of YAC clones of the 5q21 region were cloned by screening with markers for the region. Six genes expressed in normal colon cells and in colorectal, lung and bladder **tumors** were found in the region. These genes were: the FER gene at 5q11-23 similar to the v-abl gene; TB1 showing some similarity to brown adipose tissue uncoupling proteins; MCC and TB2; and **APC**. A cDNA from the **APC** gene had an open reading frame of 8,535 nucleotides that encoded a protein with some similarity to myosins and intermediate filament proteins and to the ral2 gene product of yeast. The assocn. of these genes and mutant alleles with colorectal **cancer** was studied by std. methods. The gene that showed the greatest no. of germline and somatic mutations was **APC** and the characterization of a no. of the mutations is described.

L39 ANSWER 48 OF 50 MEDLINE

92213691 Document Number: 92213691. PubMed ID: 1725227. Functionally active protein C inhibitor/plasminogen activator inhibitor-3 (PCI/PAI-3) is secreted in seminal vesicles, occurs at high concentrations in human seminal plasma and complexes with prostate-specific antigen. Espana F; Gilabert J; Estelles A; Romeu A; Aznar J; Cabo A. (Research Center, Hospital Universitario La Fe, Valencia, Spain.) THROMBOSIS RESEARCH, (1991 Nov 1) 64 (3) 309-20. Journal code: VRN; 0326377. ISSN: 0049-3848. Pub. country: United States. Language: English.

AB Protein C inhibitor (PCI) is a heparin-dependent serpin present in a native form in plasma at concentrations of 5 micrograms/mL. In vitro, PCI inhibits activated protein C (**APC**), thrombin, plasma kallikrein (KK) and urokinase-(uPA) and tissue-type plasminogen activator (tPA), and we have shown in vivo inhibition of **APC**, uPA and KK by PCI. In order to further characterize the physiological role of PCI, we have

measured the level of PCI in several biological fluids. PCI antigen was assayed by ELISA and PCI activity was measured by its capability to form complexes with APC in the presence of heparin. Seminal plasma from voluntary donors had PCI levels (160 +/- 20 micrograms/mL, mean +/- SD) about 30 or 40 times higher than those found in blood plasma. Patients under a fertilization program had significantly reduced PCI seminal levels (110 +/- 35 micrograms/mL). Seminal plasma PCI retained about 45% of its activity immediately after ejaculation, and the activity rapidly decreased following incubation of seminal plasma at 37 degrees C, in parallel with the appearance of complexes of PCI with prostate-specific antigen (PSA). PCI was present in seminal vesicle secretion, obtained by autopsy, at concentration similar to that observed in semen, was mostly active and was not inactivated by incubation of secretion at 37 degrees C. The mean functional and antigen levels of PCI in **urine** from normal donors were 0.58 and 0.25 micrograms/mL, respectively, whereas in saliva these levels were 20 and 0.8 ng/mL, respectively. Amniotic fluid contained PCI antigen levels of 2.1 +/- 0.2 microgram/mL. These results show that PCI is secreted in the seminal vesicles in a functional form, and suggest that PSA, a major secretory component of the prostate, is responsible for its inactivation. They also suggest a physiological role of PCI in reproduction, and show that PCI is present in various biological fluids.

L39 ANSWER 49 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
 91327358 EMBASE Document No.: 1991327358. **Cancer** of the ureter in a Negro population. Aghaji A.E.; Mbonu O.O.. Department of Surgery, University of Nigeria Teaching Hospital, Enugu, Nigeria. Journal of the Royal College of Surgeons of Edinburgh 36/5 (306-308) 1991. ISSN: 0035-8835. CODEN: JRCSAC. Pub. Country: United Kingdom. Language: English. Summary Language: English.

L39 ANSWER 50 OF 50 MEDLINE
 91111957 Document Number: 91111957. PubMed ID: 1899165.
 Immunohistochemical characterization of HLA-DR-antigen positive **dendritic cells** in phaeochromocytomas and paragangliomas as a prognostic marker. Furihata M; Ohtsuki Y. (Department of Pathology, Kochi Medical School, Japan.) VIRCHOWS ARCHIV. A, PATHOLOGICAL ANATOMY AND HISTOPATHOLOGY, (1991) 418 (1) 33-9. Journal code: XD1; 8302198. ISSN: 0174-7398. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Twelve cases of phaeochromocytoma (PCC) and four cases of paraganglioma (PGG) were studied by immunohistochemistry and immunoelectron microscopy in order to demonstrate HLA-DR (Ia)-antigen-positive **dendritic cells** (IaDCs). Dense infiltration of IaDCs was detected in the majority of PCCs revealing high urinary or serum catecholamine levels, but in aggressively growing PCCs, a familial PCC and all PGGs, few IaDCs were demonstrated. Interestingly, these IaDCs were negative for S-100 protein. Although S-100-protein-positive sustentacular-like cells (SCs), morphologically similar to IaDCs, were also present, these were clearly distinguished from IaDCs by our double immunostaining method. Ultrastructurally, IaDCs had smooth or slightly indented nuclei and contained a moderate amount of endoplasmic reticulum, small mitochondria and vacuoles, extending elongated cytoplasmic processes. These results suggest that determination of the quantity of IaDCs is a highly effective method of assessing the character of PCCs, in particular, their prognosis.

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L60 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

2002:143198 Method for inducing an anti-tumor and anti-cachexia
immune response in mammals. Riordan, Neil H.

(USA). U.S. Pat. Appl. Publ. US 20020022036 A1 20020221, 9 pp.
(English). CODEN: USXXCO. APPLICATION: US 2001-781023 20010209.
PRIORITY: US 2000-PV226752 20000821.

AB The invention relates to inducing an immune response toward tumor assocd.
antigens and in particular to the administration of high mol. wt. isolates
of autologous urine either alone, with adjuvants, or with antigen
presenting cells. The antigen presenting cells have been cocultured with
isolates of autologous urine. The invention can also be used to treat
cachexia in cancer or AIDS patients.

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L62 26 FILE CAPLUS
L63 69 FILE EMBASE
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TOTAL FOR ALL FILES

L67 191 IMMUNE RESPONSE AND URINE AND (CANCER OR TUMOR OR TUMOR OR CACHEX?)

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intravenous? or intraderm? or subcutan? or intralymphat?)

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 L71 24 FILE BIOSIS
 L72 1 FILE JICST-EPLUS
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L74 148 L67 AND (TREAT? OR THERAP? OR INDUC? OR INJECT? OR INTRA MUSCUL?
 OR INTRAVENOUS? OR INTRADERM? OR SUBCUTAN? OR INTRALYMPHAT?)

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 L83 3 FILE CAPLUS
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L89 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1

2001:565267 Document No. 135:165528 Protein and cDNA sequences of prostate and testis specific protein 84P2A9 highly expressed in prostate and other **cancers**. Jakobovits, Aya; Afar, Daniel E. H.; Challita-Eid, Pia M.; Levin, Elana; Mitchell, Steve Chappell; Hubert, Rene S. (Urogenesys, Inc., USA). PCT Int. Appl. WO 2001055391 A2 20010802, 149 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US2651 20010126. PRIORITY: US 2000-PV178560 20000126.

AB A novel, largely prostate and testis-related gene (designated 84P2A9) and its encoded protein is described. While 84P2A9 exhibits prostate and testis specific expression in normal adult tissue, it is aberrantly overexpressed in multiple **cancers** including prostate, testis, kidney, brain, bone, skin, ovarian, **breast**, pancreas, colon, lymphocytic and lung **cancers**. Over-expression of 84P2A9, relative to normal, is obsd. in prostate **cancer** xenografts initially derived from a prostate **cancer** lymph node metastasis

and in SCID mice. A full-length 84P2A9 cDNA encodes a 504 amino acid protein with some homol. to the KIAA1152 human brain protein and **tumor** suppressor protein LUCA15. The 84P2A9 gene is localized to human chromosome 1q32.3 (D1S1602-D1S217). Thus, the 84P2A9 gene encodes a **tumor** antigen which may be useful as a diagnostic, staging and/or prognostic marker for, and/or may serve as a target for various approaches to the **treatment** of various **cancers** expressing 84P2A9. The 84P2A9 gene or fragment thereof, or its encoded protein or a fragment thereof may be used to elicit an **immune response**.

L89 ANSWER 2 OF 13 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-607650 [69] WPIDS

AB WO 200173437 A UPAB: 20011126

NOVELTY - Detecting (M) presence of an antigen, antibody, or both antigen and antibody in immune complexes, involves capturing a circulating immune complex from a sample, dissociating the captured immune complex, re-associating the dissociated immune complex with a reference material to form a reformed immune complex, and detecting and quantitating the reference material in the reformed immune complex.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a well (I) for use in a spectrophotometer having a light source, where (I) comprises one or more surface area increasing members, and is made of a material that remains substantially optically transparent in an appropriate substrate buffer; and

(2) a kit (II) for detecting antigen, antibody, or both antigen and antibody in immune complexes in a mixture, comprising a marker, and a reference material, where the reference material is selected from antibodies and receptors.

USE - (M) is useful for detecting the presence of antigen, antibody, or both antigen and antibody in immune complexes from a sample (claimed) for diagnosing numerous diseases. (M) is useful to detect proteins that the immune system recognizes as important in disease. (M) is useful for a host of diseases and conditions for which markers for the disease or conditions have been identified, and to elucidate and/or screen for the humoral **immune response's** targets within selected individuals, groups of individuals with shared diseases or conditions, and microarray data suggesting sets of activated genes or altered proteomic profiles. A kit (II) is useful for detection of many types of diseases, such as autoimmune diseases, oncology (**cancer**) and infectious diseases.

ADVANTAGE - (M) detects markers that current tests miss and detects initial and recurring **tumors** earlier with less false positive and negative results, and as a result redefines the way science deals with proteins (selective proteomics) and accelerates the development of such products as disease diagnostics, prognostic markers and **therapeutics**. (M) detects various proteins earlier and more precisely than currently available diagnostic techniques as (M) uses the body's ability to be immune based. (M) allows the physician to see how well or poorly the patient's immune system is dealing with the disease. (M) aids in monitoring recurrence because there is no test available that reliably detects recurrent **breast cancer** until the disease is incurable. (M) also finds novel **tumor**-antigens because many of the best selling drugs either act by targeting proteins or are proteins. (M) finds evidence of diseases in ways existing kits cannot, and has a profound effect on the way diseases are diagnosed, recurrences are detected and molecular **therapeutic** targets are discovered. (M) allows individuals to be **treated** with drug **therapy** sooner and more accurately, thus enhancing a patient's chance for recovery. (M) is beneficial to all patient subtypes, and especially beneficial for younger patients for whom current diagnostic modalities, such as mammograms, are not very sensitive. (M) supports a range of blood

tests, not only for **breast cancer**, but for various **cancers**, and for autoimmune disorders and infectious diseases.
Dwg.0/4

L89 ANSWER 3 OF 13 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-514676 [56] WPIDS

CR 1998-531576 [45]

AB WO 200159158 A UPAB: 20011227

NOVELTY - Diagnosing **cancer** (M1) comprises detecting stratum corneum chymotrypsin enzyme (I).

DETAILED DESCRIPTION - Diagnosing **cancer** (M1) comprises:

(a) obtaining a biological sample; and
(b) detecting stratum corneum chymotrypsin enzyme (I), where the presence of (I) is indicative of the presence of **cancer**.

INDEPENDENT CLAIMS are also included for the following:

(1) a method (M2) for detecting malignant hyperplasia in a sample comprising:

(a) isolating mRNA from the sample; and

(b) detecting the mRNA of (I);

(2) a method (M3) for detecting malignant hyperplasia in a sample comprising:

(a) isolating protein from the sample; and

(b) detecting the protein of (I);

(3) a method (M4) for inhibiting expression of endogenous (I) in a cell comprising introducing a vector (II) into a cell, where (II) comprises a gene encoding (I) in opposite orientation linked to elements necessary for expression, where expression of (II) produced antisense mRNA of (I) which hybridizes to endogenous mRNA of (I) to inhibit its expression;

(4) a method (M5) of inhibiting (I) in a cell comprising introducing an antibody (III) specific for (I), where binding of (III) inhibits (I);

(5) a method (M6) of targeted **therapy** comprising administering a compound which has a targeting moiety and a **therapeutic** moiety where the **therapeutic** moiety is specific for (I);

(6) a method (M7) of vaccinating against (I) comprising inoculating with (I) or its fragment which lacks protease activity and elicits an **immune response**;

(7) a method (M8) of producing immune-activated cells directed towards (I) comprising exposing dendritic cells to (I) or its fragment which lacks protease activity in order to activate the dendritic cells;

(8) an oligonucleotide (IV) having a sequence complementary to the fully defined 969 base pair sequence given in the specification (N1);

(9) a composition comprising (IV); and

(10) a method (M9) of screening for compounds that inhibit (I) comprising:

(a) contacting a sample which comprises (I) with a compound; and

(b) assaying for activity of (I), where a decrease in activity in the presence of the compound compared to the activity in the absence of the compound is indicative that the compound inhibits (I).

ACTIVITY - Cytostatic.

No supporting data given.

MECHANISM OF ACTION - Vaccine; antisense **therapy** (claimed).

No supporting data given.

USE - The method is useful for diagnosing **cancer** (claimed).

The oligonucleotide (IV) may be used to **treat** a **cancer** selected from ovarian, **breast**, lung, colon, prostate and other **cancers** in which (I) is overexpressed (claimed).

Dwg.0/19

L89 ANSWER 4 OF 13 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-496835 [54] WPIDS
CR 1998-531576 [45]
AB WO 200154712 A UPAB: 20011220

NOVELTY - Diagnosing **cancer** in an individual comprising:

(a) obtaining a biological sample from an individual; and
(b) detecting PUMP-1 (undefined) protease in the sample, where the presence of PUMP-1 in the sample is indicative of the presence of **cancer** in the individual and the absence of PUMP-1 in the individual is indicative of the absence of **cancer** in the individual, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) detecting malignant hyperplasia comprising isolating mRNA or protein from the sample and detecting PUMP-1 mRNA or protein in the sample, where the presence of PUMP-1 in the sample is indicative of the presence of malignant hyperplasia in the individual and the absence of PUMP-1 in the individual is indicative of the absence of malignant hyperplasia in the individual;

(2) inhibiting expression of endogenous PUMP-1 in a cell comprising introducing a vector into a cell, where the vector comprises a PUMP-1 gene in opposite orientation operably linked to elements necessary for expression, where expression of the vector in the cell produces PUMP-1 antisense mRNA, and where the PUMP-1 antisense mRNA hybridizes to endogenous PUMP-1 mRNA, thus inhibiting expression of endogenous PUMP-1 in the cell;

(3) inhibiting PUMP-1 protein in a cell comprising introducing an antibody into a cell, where the antibody is specific for a PUMP-1 protein or its fragment, and binding of the antibody to the PUMP-1 protein inhibits the PUMP-1 protein;

(4) targeted **therapy** to an individual comprising administering a compound to an individual, where the compound has a targeting group and a **therapeutic** group, where the targeting group is specific for PUMP-1;

(5) vaccinating an individual against PUMP-1 comprising inoculating an individual with a PUMP-1 protein or its fragment, where the PUMP-1 protein or its fragment lack PUMP-1 protease activity, where the inoculation with the PUMP-1 protein or its fragment elicits an **immune response** in the individual against PUMP-1;

(6) producing immune-activated cells directed toward PUMP-1 comprising exposing dendritic cells to a PUMP-1 protein or its fragment, where the PUMP-1 protein or its fragment lacks PUMP-1 protease activity, and where the exposure to the PUMP-1 protein or its fragment activates the dendritic cells, thus producing immune-activated cells directed toward PUMP-1;

(7) an oligonucleotide having a sequence complementary to a fully defined 1078-base pair (bp) DNA sequence as given in the specification;

(8) **treating** a neoplastic state in an individual in need of such **treatment** comprising administering to the individual the oligonucleotide;

(9) screening for compounds that inhibit PUMP-1 activity comprising:

(a) contacting a sample with a compound, where the sample comprises PUMP-1 protein; and

(b) assaying for PUMP-1 protease activity, where a decrease in the PUMP-protease activity in the presence of the compound relative to PUMP-1 protease activity in the absence of the compound indicatives the compound inhibits PUMP-1 activity and

(10) detecting ovarian malignant hyperplasia in a biological sample comprises:

(a) isolating the proteases or protease mRNA present in the biological sample; and

(b) detecting specific proteases or protease mRNA present in the

biological sample, where the proteases are hepsin, protease M, complement factor B, stratum corneum chymotrypsin enzyme (SCCE), other serine proteases, cathepsin L or PUMP-1.

ACTIVITY - Cytostatic. No supporting data is given.

MECHANISM OF ACTION - Gene **therapy**; vaccine.

USE - The method is useful for the early detection or diagnosis of ovarian **cancer** and other neoplastic state or malignancies (e.g. lung **cancer**, prostate **cancer**, colon **cancer** or other **cancers** in which PUMP-1 is overexpressed). The method is also useful for diagnosing whether an individual has **cancer**, is suspected of having **cancer** or is at risk of getting **cancer**. The PUMP-1 proteins are also useful for vaccinating against neoplastic states. The oligonucleotide is useful for **treating** a neoplastic state such as lung **cancer**, prostate **cancer**, colon **cancer** or other **cancers** in which PUMP-1 is overexpressed (all claimed).
Dwg.0/21

L89 ANSWER 5 OF 13 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-273769 [28] WPIDS

AB WO 200127257 A UPAB: 20010522

NOVELTY - DNA (I) encoding a **tumor** antigen-derived gene (TADG-16) protein, is new.

DETAILED DESCRIPTION - DNA (I) encoding a **tumor** antigen-derived gene (TADG-16) protein comprising:

- (a) isolated DNA which encodes a TADG-16 protein;
- (b) isolated DNA which hybridizes under high stringency conditions to (a); or
- (c) isolated DNA differing from (a) and (b) in codon sequence due to the degeneracy of the genetic code, is new.

INDEPENDENT CLAIMS are also included for the following:

- (1) an antisense oligonucleotide (II) having a complementary sequence to (I);
- (2) a vector (III) comprising (I);
- (3) a host cell transfected with (III);
- (4) isolated and purified TADG-16 protein (IV) coded for by (I);
- (5) an antibody (V) specific for (IV) or its fragment;
- (6) detecting TADG-16 mRNA in a sample comprising contacting a sample with a probe specific for TADG-16 and detecting binding of the probe to TADG-16 mRNA;
- (7) detecting TADG-16 protein in a sample comprising contacting a sample with (V) and detecting binding of (V) to TADG-16 mRNA;
- (8) a kit for detecting TADG-16 mRNA comprising an oligonucleotide probe specific for TADG-16;
- (9) a kit for detecting TADG-16 protein comprising (V);
- (10) inhibiting endogenous expression of TADG-16 in a cell comprising introducing (III) into a cell, where expression of (III) produces TADG-16 antisense mRNA in the cell, which hybridizes to endogenous TADG-16 mRNA;
- (11) inhibiting a TADG-16 protein in a cell comprising introducing (V) into a cell;
- (12) **treating** (M1) a neoplastic state in an individual comprising administering (II);
- (13) vaccinating (M2) an individual against TADG-16 comprising inoculating an individual with a TADG-16 protein or its fragment, where the protein or fragment lack TADG-16 protease activity and the inoculation elicits an **immune response** in the individual;
- (14) diagnosing (M3) **cancer** in an individual comprising obtaining a biological sample from the individual and detecting TADG-16 in the sample, where the presence of TADG-16 is indicative of the presence of carcinoma;
- (15) screening for compounds that inhibit TADG-16 comprising

contacting a TADG-16 protein containing sample with a compound and assaying for TADG-16 protease activity, where a decrease in activity in the presence of the compound relative to activity in the absence of the compound is indicative of a compound that inhibits TADG-16; and

(16) targeted **therapy** (M4) to an individual comprising administering a compound with a targeting group specific for TADG-16 and a **therapeutic** group.

ACTIVITY - Cytostatic. No supporting data given.

MECHANISM OF ACTION - Gene **therapy**; vaccine.

USE - (II) is useful for **treating various cancers**, including ovarian, **breast**, lung, colon and prostate. TADG-16 protein or its fragments are useful for vaccinating an individual against TADG-16. (I), (IV) and (V) are useful for the diagnosis of **cancer** (all claimed).

Dwg.0/6

L89 ANSWER 6 OF 13 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-081050 [09] WPIDS

AB WO 200104309 A UPAB: 20010213

NOVELTY - An isolated T-cell receptor gamma (TCR gamma) Alternate Reading frame Protein (TARP), is new.

DETAILED DESCRIPTION - An isolated polypeptide (I) comprising an amino acid sequence which is TARP, an immunogenic fragment of TARP, a polypeptide with at least 90% sequence identity to TARP and is specifically recognized by an antibody which specifically recognizes TARP or a polypeptide which has at least 90% sequence identity with TARP and when processed and presented in the context of Major Histocompatibility Complex molecules activates T lymphocytes against cells which express TARP.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated, recombinant nucleic acid molecule (II) comprising a nucleotide sequence encoding (I);

(2) a method for detecting a prostate cell of epithelial origin in a male or a **breast cancer** cell in a female comprising detecting in a cell from the male or female a nucleic acid transcript encoding TARP or detecting TARP produced by translation of the transcript where detection of the transcript or protein in the cell from the male identifies the cells as a prostate epithelial cell and in the cell from the female as a **breast cancer** cell;

(3) an antibody which specifically binds to an epitope of a TARP; and

(4) a method for modulating the levels of TARP in a cell comprising introducing into the cell a ribozyme which specifically cleaves a TARP-encoding nucleic acid, an antisense oligonucleotide which specifically binds a TARP-encoding nucleic acid, a DNA binding protein which specifically binds a TARP-encoding nucleic acid or a nucleic acid encoding TARP operatively linked to a promoter.

ACTIVITY - Cytostatic.

No biological data is given.

MECHANISM OF ACTION - Gene **therapy**.

USE - TARP proteins and nucleic acids are used to detect prostate **cancer** in males and **breast cancer** in females (claimed).

(I), (II), an antigen presenting cell pulsed with a polypeptide comprising an epitope of TARP or cells sensitized in vitro to (I) or an expression vector expressing a polypeptide comprising an epitope of a TARP protein, where the expression vector is in a recombinant cell, can be administered to a subject who suffers from **breast cancer** or prostate **cancer**, including females who have not been diagnosed with **breast cancer** (claimed) to raise or heighten an **immune response** to prostate or **breast cancer**.

Dwg.0/14

L89 ANSWER 7 OF 13 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2000-533263 [48] WPIDS

CR 2001-647267 [72]

AB WO 200052044 A UPAB: 20020105

NOVELTY - DNA fragment (I) encoding a transmembrane serine protease called **tumor** associated differentially-expressed gene 12 (TADG12) protein, is new.

DETAILED DESCRIPTION - DNA fragment (I) encoding **tumor** associated differentially-expressed gene 12 (TADG12) protein is selected from:

- (a) an isolated DNA fragment which encodes a TADG12 protein;
- (b) an isolated DNA fragment which hybridizes to isolated DNA fragment of (a) and encodes a TADG12 protein;
- (c) an isolated DNA fragment differing from the fragments (a) and (b) in codon sequence due to the degeneracy of the genetic code which encodes a TADG12 protein.

INDEPENDENT CLAIMS are also included for the following:

- (1) a vector comprising (I) and regulatory elements needed for the expression of the DNA in a cell;
- (2) a host cell transfected with the vector of (1) expressing a TADG12 protein;
- (3) an antisense oligonucleotide directed against (I);
- (4) an isolated and purified TADG12 protein (II) coded for by (I);
- (5) method for detecting expression of (II) comprising contacting mRNA obtained from a cell with a labeled hybridization probe and detecting hybridization of the probe with the mRNA;
- (6) antibody directed against (II);
- (7) method for diagnosing **cancer** or malignant hyperplasia in an individual comprising detecting a TADG12 protein in a biological sample from the individual which is indicative of the presence of a **cancer** or malignant hyperplasia in an individual;
- (8) method for detecting malignant hyperplasia in an individual comprising detecting a TADG12 mRNA in a sample from the individual which is indicative of the presence of malignant hyperplasia in an individual;
- (9) method of inhibiting expression of endogenous TADG12 mRNA in a cell by introducing a vector comprising a DNA fragment of TADG12 in opposite orientation operably linked to elements needed for expression, where expression of the vector in the cell produces TADG12 antisense mRNA that hybridizes to endogenous TADG12 mRNA, inhibiting its expression in the cell;
- (10) method of inhibiting expression of TADG12 protein in a cell by introducing an antibody directed against TADG12 protein into the cell;
- (11) a method (III) of targeted **therapy** to an individual comprising administering a compound to an individual that has a targeting group specific to TADG12 protein and a **therapeutic** group; and
- (12) a method of vaccinating an individual against TADG12 by inoculating an individual with a TADG12 protein or fragment that lacks TADG12 activity and elicits an **immune response** in the individual.

ACTIVITY - Cytostatic.

No biological data is given.

MECHANISM OF ACTION - Vaccine; antisense gene **therapy**.

USE - (I) and (II) are used in diagnosing malignant hyperplasia and **cancers** e.g. ovarian, **breast**, lung, colon, prostate or other **cancer** where TADG12 protein is overexpressed (claimed). TADG12 is particularly useful as a **tumor** marker for indicating early disease.

Ovarian, **breast**, lung, colon, prostate or other **cancer** where TADG12 protein is overexpressed can be **treated** by targeting **therapeutic** groups e.g. radioisotope, toxin, chemotherapeutic agent, immune stimulant or cytotoxic

agent to the **cancer** using antibodies directed against TADG12 protein (claimed). TADG12 proteins or fragments can be used to vaccinate an individual with **cancer**, suspected of having a **cancer** or at risk of getting **cancer** (claimed).

ADVANTAGE - A transmembrane serine protease not previously identified is disclosed.

Dwg.0/9

L89 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
1999:737073 Document No. 131:350237 Detection of antibody response to **tumor** markers for diagnostic and prognostic assessment of **cancer**. Robertson, John Forsyth Russell; Graves, Catherine Rosamund Louise; Price, Michael Rawling (The University of Nottingham, UK). PCT Int. Appl. WO 9958978 A2 19991118, 81 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1479 19990511. PRIORITY: GB 1998-10040 19980511.

AB The authors disclose the detn. of the humoral **immune response** to circulating **tumor** marker proteins. The presence of complexes between the **tumor** marker antigens and any autoantibodies to the antigens present in a sample are detected and provide an assessment of the presence of **cancer**, its reoccurrence after **treatment**, and prognosis. In one example, antibodies to MUC-1, c-erbB2, c-myc, and p53 were shown to be indicative not only of **cancer** onset but also metastatic reoccurrence.

L89 ANSWER 9 OF 13 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1999-229552 [19] WPIDS
AB WO 9914372 A UPAB: 19990518

NOVELTY - Novel methods for detecting, diagnosing, staging, monitoring, prognosticating, in vivo imaging, preventing, **treating** or determining a predisposition to diseases or conditions of the urinary tract, particularly **cancer**, use products derived from keratin/cytokeratin, cellular apoptosis susceptibility or mat-8-specific polynucleotides (PNs).

DETAILED DESCRIPTION - A novel method of detecting the presence of urinary tract disease (UTD) in an individual comprises:

(a) providing a test sample from the individual and contacting the test sample with at least one keratin/cytokeratin (K/C), cellular apoptosis susceptibility (CAS) or mat-8-specific PN or complement, where the K/C, CAS, or mat-8-specific PN has at least 50% identity with a PN selected from sequences (I)-(XIII) of 1048, 2235, 1828, 1435, 2283, 1407, 1493, 1724, 1602, 1677, 1709, 3147, and 510 nucleotides, respectively, and fragments or complements; and

(b) detecting the presence of target K/C, CAS or mat-8-PNs in the test sample which bind to the K/C, CAS or mat-8-specific PN as an indication of UTD in the individual.

INDEPENDENT CLAIMS are also included for:

(1) detecting the presence of UTD in an individual comprising:

(a) providing a test sample from the individual and performing reverse transcription on the sample using at least one primer to produce cDNA;

(b) amplifying the cDNA obtained from (a) using K/C, CAS, or mat-8 oligonucleotides (ONs) as sense and antisense primers to obtain K/C, CAS or mat-8 amplicon; and

(c) detecting the presence of the K/C, CAS, or mat-8 amplicon as an indication of UTD in the individual, where the K/C, CAS or mat-8 ONs used

in (a) and (b) have at least 50% identity with a sequence selected from sequences (I)-(XIII), and fragments or complements;

(2) detecting the presence of UTD in an individual comprising:

(a) providing a test sample from the individual and contacting the test sample with at least one K/C, CAS or mat-8 ON as a sense primer and with at least one K/C, CAS, or mat-8 ON as an antisense primer and amplifying to obtain a first stage reaction product;

(b) contacting the first stage reaction product with at least one other K/C, CAS, or mat-8 ON to obtain a second stage reaction product, with the proviso that the other K/C, CAS, or mat-8 ON is located 3' to the K/C, CAS, or mat-8 ONs used in (a) and is complementary to the first stage reaction product; and

(c) detecting the second stage reaction product as an indication of UTD in the individual where the K/C, CAS, or mat-8 ONs used in (a) and (b) have at least 50% identity with a sequence selected from sequences (I)-(XIII), and fragments or complements;

(3) a test kit useful for detecting UTD comprising a container containing at least one K/C, CAS, or mat-8 PN having at least 50% identity with a sequence selected from sequences (I)-(XIII), and fragments or complements;

(4) a specific binding molecule which specifically binds to a K/C, CAS, or mat-8 epitope which is derived from a polypeptide encoded by a nucleic acid sequence having at least 50% identity with a sequence selected from sequences (I)-(XIII), and fragments or complements;

(5) a test kit useful for detecting UTD comprising a container containing a K/C, CAS, or mat-8 polypeptide encoded by a nucleic acid sequence having at least 50% identity with a sequence selected from sequences (I)-(XIII), and fragments or complements;

(6) a test kit useful for detecting UTD in a test sample comprising a container containing a specific binding molecule which specifically binds to an epitope from a K/C, CAS, or mat-8 polypeptide encoded by a nucleic acid sequence having at least 50% identity with a sequence selected from sequences (I)-(XIII) and fragments or complements;

(7) detecting the presence of antigen indicative of UTD in an individual comprising:

(a) providing a test sample from the individual and contacting the test sample with a specific binding molecule which specifically binds to an epitope of a K/C, CAS, or mat-8 antigen selected from a polypeptide encoded by a nucleic acid sequence having at least 50% identity with a sequence selected from sequences (I)-(XIII), and fragments or complements, where the contacting is performed for the formation of binding molecule/antigen complexes; and

(b) detecting the presence of the complexes as an indication of UTD in the individual;

(8) detecting the presence of antibody indicative of UTD in an individual comprising:

(a) providing a test sample from the individual and contacting the test sample with a specific binding molecule which specifically binds to an epitope of a K/C, CAS, or mat-8 polypeptide selected from a polypeptide encoded by a nucleic acid sequence having at least 50% identity with a sequence selected from sequences (I)-(XIII), and fragments or complements, where the contacting is performed to allow antigen/antibody complexes to form; and

(b) detecting the presence of the complexes as an indication of UTD in the individual;

(9) producing antibodies which specifically bind to K/C, CAS, or mat-8 antigen, comprising administering to an individual an isolated immunogenic polypeptide or fragment to elicit an **immune response**, where the immunogenic polypeptide comprises at least one K/C, CAS, or mat-8 epitope derived from a polypeptide encoded by a nucleic acid molecule having at least 50% identity with a sequence selected from sequences (I)-(XIII) and fragments or complements; and

(10) a method similar to (9), comprising administering to an individual a plasmid comprising a sequence which encodes at least one K/C, CAS, or mat-8 epitope derived from a polypeptide encoded by a nucleic acid molecule as in (9) (all sequences are given in the specification).

USE - The PNs and polypeptides are useful for detecting, diagnosing, staging, monitoring, prognosticating, in vivo imaging, preventing or **treating**, or determining predisposition to diseases or conditions of the urinary tract such as urinary tract **cancers**.

Dwg.0/1

L89 ANSWER 10 OF 13 MEDLINE DUPLICATE 3
1999249567 Document Number: 99249567. PubMed ID: 10235488. Cellular and humoral **immune responses** to MUC1 mucin and tandem-repeat peptides in ovarian **cancer** patients and controls. Snijdwint F G; von Mensdorff-Pouilly S; Karuntu-Wanamarta A H; Verstraeten A A; van Zanten-Przybysz I; Hummel P; Nijman H W; Kenemans P; Hilgers J. (Department of Obstetrics and Gynaecology, Academic Hospital Vrije Universiteit, Amsterdam, The Netherlands.. snijdwint@azvu.nl) . CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1999 Apr) 48 (1) 47-55. Journal code: CN3; 8605732. ISSN: 0340-7004. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The objective of this study was to demonstrate the presence of proliferative T cell responses to human polymorphic epithelial mucin (MUC1) and its tandem-repeat peptides in peripheral blood mononuclear cells (PBMC) from ovarian **cancer** patients and from controls and to correlate these cellular responses to a humoral response to MUC1. PBMC were obtained from 6 healthy women, from 13 women in the third trimester of pregnancy and from 21 ovarian **cancer** patients. Only 1 of the 6 healthy women showed a weak primary proliferative response (stimulation index, SI <2) to a 20-mer MUC1 tandem-repeat peptide in the presence of interleukin-2 (IL-2). In PBMC from 5/13 pregnant women (38%) a weak response could be **induced** by the 20-mer and/or 60-mer tandem-repeat peptides (SI < or =3.0) and in PBMC from 8/15 ovarian **cancer** patients (53%) 20-mer and/or 60-mer MUC1 tandem-repeat peptides **induced** primary responses (SI < or =5.4). MUC1 mucin purified from a **breast tumor** cell line and/or from **urine** of a healthy donor had a relatively strong stimulating effect (SI < or =19) on PBMC from 4 of 16 ovarian **cancer** patients (25%). In contrast, in PBMC of 9 ovarian **cancer** patients stimulated by the addition of a Candida albicans extract, MUC1 mucin strongly inhibited proliferation. This inhibition could partially be abrogated by the addition of IL-2. MUC1 (CA 15.3 assay) and free circulating MUC1 IgG and IgM antibodies (PEM.CIg assay) were determined in the plasma of all subjects. The MUC1 and the free circulating MUC1 IgG antibody plasma levels were significantly higher in the ovarian **cancer** patients than in the healthy women. Although no significant correlations were found between MUC1 mucin, MUC1 Ab plasma levels and the individual proliferative responses to the MUC1 antigens, an association may exist between them, since all three are significantly higher in the ovarian **cancer** patients than in the healthy women.

L89 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
1995:368336 Document No. 122:182115 Targeting of **tumors** with murine and reshaped human monoclonal antibodies against placental alkaline phosphatase: immunolocalization, pharmacokinetics and **immune response**. Kalofonos, H.P.; Kosmas, C.; Hird, V.; Snook, D.E.; Epenetos, A.A. (Patras, 26441, Greece). Eur. J. Cancer, Part A, 30A(12), 1842-50 (English) 1994. CODEN: EJCTEA.
AB Anti-**tumor** monoclonal murine and humanized (reshaped human) antibodies (H17E2 and Hu2PLAP, resp.) against placental alk. phosphatase (PLAP), radioactively labeled with indium-111 (111In) and iodine-123 (123I), were evaluated for their ability to localize mainly testicular and

ovarian **tumors** in sequential pilot studies of the Hammersmith Oncol. Group. Patients with active primary and/or metastatic testicular **cancer** were studied with the [¹¹¹In]- or [¹²³I]H17E2 antibody. Patients with testicular **cancer** were studied with the same antibody after being rendered free of disease after **induction** chemotherapy and surgical resection of residual **tumor**. Addnl. patients, 2 with ovarian **cancer** and 1 with testicular seminoma, were studied with [¹¹¹In]H17E2 via a macrocyclic chelating agent (DOTA). Patients, 5 with ovarian **cancer**, 1 with **breast cancer**, and 1 with gastric **cancer**, received the reshaped human Hu2PLAP antibody [¹¹¹In]DOTA labeled. One of these was imaged twice, with H17E2- and Hu2PLAP-DOTA-¹¹¹In, resp. In the initial 33 patients with active primary and/or metastatic testicular **cancer**, the presence of **tumor** was confirmed and correlated well with conventional radiol. diagnostic methods, and in addn., the antibody scan revealed the presence of active disease in 2 patients with neg. conventional imaging, but elevated serum **tumor** markers. In the 8 patients with complete remission (CR), imaging studies with the radiolabeled antibody did not show any localization. The best images were obtained at 24 and 48 h after the [¹²³I]- and [¹¹¹In]H17E2, resp. None of these patients developed human anti-mouse antibody responses (HAMA). Successful imaging with the reshaped human antibody, Hu2PLAP-DOTA-¹¹¹In, was seen in 3 patients with PLAP-pos. **tumors** (2 ovarian and 1 gastric **cancer**). The 3 neg. patients were 1 in complete remission, 1 with PLAP-neg. **tumor** and 1 who cleared the Hu2PLAP antibody immediately after infusion due to the presence of anti-chelating agent (anti-DOTA) antibodies from a previous H17E2-DOTA-¹¹¹In scan. One patient with PLAP-neg. **breast** carcinoma had a false-pos. scan with Hu2PLAP, showing localization to the pleural effusion. Antibody pharmacokinetics showed a mean t_{1/2}.beta. = 73.1 +/- 30.2 h (n = 5) for Hu2PLAP vs. t_{1/2}.beta. = 27.2 +/- 5.9 h (n = 3) for H17E2 (P < 0.05). Patients receiving Hu2PLAP were excluded due to the rapid clearance of the radiolabel as a result of the presence of high HAMA and anti-chelate antibody levels, resp. At 96 h, the mean cumulative **urine** excretion of ¹¹¹In was 11 +/- 8% for Hu2PLAP vs. 14 +/- 5% for H17E2. HAMA developed in 1 patient undergoing sequential imaging with both antibodies, and in another who already had HAMA after i.p. monoclonal antibody **therapy** for ovarian **cancer**. Antibodies to the chelating agent developed in 3 patients. In conclusion, immunolocalization of PLAP-pos. **tumors** is feasible with both murine and reshaped human monoclonal antibodies. The sensitivity and specificity of the method appear to be very high in this pilot study, and, in view of the absence of toxicity, the diagnostic contribution of this approach should be evaluated prospectively.

L89 ANSWER 12 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
 83247595 EMBASE Document No.: 1983247595. [Diagnostic significance of neopterin, a marker of cellular **immune response**, in patients with gynecological, hematological and pediatric neoplasias]. DIAGNOSTISCHE SIGNIFIKANZ VON NEOPTERIN, EINEM MARKER DER ZELLULAREN IMMUNANTWORT, BEI PATIENTEN MIT GYNKOLOGISCHEN, HAMATOLOGISCHEN UND PADIATRISCHEN NEOPLASIEN. Hausen A.; Fuchs D.; Knosp O.; et al.. Inst. Med. Chem.-Biochem.,-Univ. Innsbruck, A-6020 Innsbruck, Austria. Arztliche Laboratorium 29/8 (243-247) 1983.
 CODEN: AEELAAH. Pub. Country: Germany. Language: German. Summary Language: English.

AB Neopterin levels were measured in the **urine** of 417 normal subjects, 224 female patients with genital carcinoma, 191 patients with hematological neoplasms, and 50 children with malignant diseases. Before the onset of **treatment** increased neopterin levels were observed in a high percentage of cases. Correlation with clinical and X-ray findings was even better during follow-up examinations. In the patients

with hematological neoplasms, neopterin values correlated with the stage of the disease whereas nearly normal values were found during remission. The results show that in certain **tumors** neopterin is a useful indicator of the course of the disease. The biological role of neopterin excretion is known in part. Increased neopterin values are found in all diseases associated with a stimulation of cellular **immune response**.

L89 ANSWER 13 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
 78160912 EMBASE Document No.: 1978160912. Homogeneous (monoclonal) immunoglobulins in **cancer**. Solomon A.. Univ. Tennessee Cent. Hlth Sci., Knoxville, Tenn., United States. American Journal of Medicine 63/2 (169-176) 1977.
 CODEN: AJMEAZ. Pub. Country: United States. Language: English.
 AB Monoclonal immunoglobulins, which are characteristic of lymphoproliferative diseases are also encountered in serum or **urine** of patients with non-reticular neoplasm or inflammatory diseases and occasionally in normal persons, especially those over 70. Hyperproteinemias caused by monoclonal immunoglobulins are found in many different histological types of neoplastic diseases, e.g. in carcinomas of the colon, the prostate, the **breast** and the lungs. M-components are more frequent in non-reticular than in reticular neoplasms. Highly sensitive methods such as agarose gel electrophoresis can demonstrate even very low concentrations of the M-gradient. Large-scale tests in patients with monoclonal immunoglobulins revealed presence of carcinomas in the absence of a myeloma in 15-30%. IgG protein was predominant. No correlation between the level of the M-gradient and the spread, course or **therapeutic** response was found in carcinomas. Non-reticular neoplasms often show mononuclear cell infiltration; plasma cells are often encountered as a reaction to the neoplasm. These contain the same monoclonal immunoglobulin as the M-component of the serum. Each immunoglobulin has a single antigen determinant which is specific of the protein. This idiotypical antigen determinant controls **tumor** growth. Immunoglobulins serve as humoral and cellular receptors of the **immune response**. They have an antibody and an effector function. The reaction on non-immunological basis with heparin is interesting. (Leibetseder - Salzburg)

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